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(54) **New diphosphonic acid compounds, processes for the preparation thereof and pharmaceutical composition comprising the same.**

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## Description

This invention relates to new diphosphonic acid compounds and pharmaceutically acceptable salts thereof.

More particularly, it relates to new diphosphonic acid compounds and pharmaceutically acceptable salts thereof which have inhibitory activities on bone resorption, to processes for the preparation thereof, to a pharmaceutical composition comprising the same and to its use as a medicament for the treatment of bone diseases characterized by abnormal bone metabolism in human beings or animals.

One object of this invention is to provide new and useful diphosphonic acid compounds and pharmaceutically acceptable salts thereof which possess inhibitory activities on bone resorption.

Another object of this invention is to provide processes for the preparation of said diphosphonic acid compounds and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising, as an active ingredient, said diphosphonic acid compounds and pharmaceutically acceptable salts thereof.

Still further object of this invention is to provide a medicament for use in the treatment of bone diseases characterized by abnormal bone metabolism such as osteoporosis, Paget's bone disease, osteolysis, hypercalcemia of malignancy and rheumatoid arthritis.

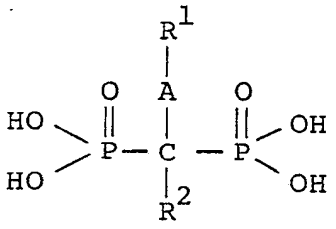
It has been known as described in U.S. Patent No. 3,906,062 that some of the alkyl ester derivatives of the object compounds as stated below have pesticidal activity. However, it has never been known that they have inhibitory activities on bone resorption.

It has been known as described in German Patent Application publication No. 2741513 that some acylaminoalkylidenediphosphonic acid compounds are useful as a polishing agent in dentifrice preparations. However, it has never been known that they have inhibitory activities on bone resorption.

Some diphosphonic acid compounds having antiinflammatory and antirheumatic activities have been known as described in European Patent Application publication No. 100718.

Some diphosphonic acid compounds which are useful for the treatment of bone diseases have been known as described in European Patent Application publication No. 170228.

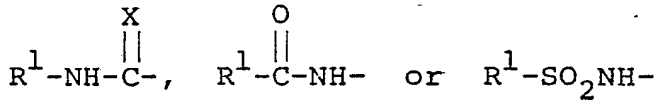
The object diphosphonic acid compounds of this invention are new and can be represented by the following general formula [I]:



[I]

wherein

$R^1$-A- is a group of the formula :



in which

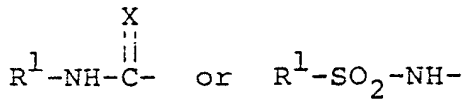
$R^1$ is aryl or a heterocyclic group, each of which may be substituted with substituent(s) selected from the group consisting of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkylthio, halo($C_1$-$C_6$)-alkyl, acyl, acylamino and halogen, or $C_1$-$C_6$ alkyl which may be substituted with a heterocyclic group optionally substituted with acyl, and

X is O or S, and

$R^2$ is hydrogen or $C_1$-$C_6$ alkyl,

provided that when $R^1$ is $C_1$-$C_6$ alkyl, then

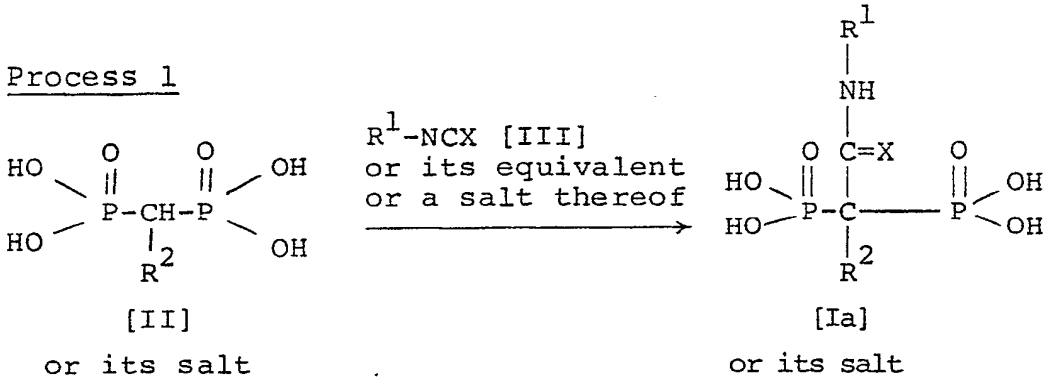
$R^1$-A- is a group of the formula :



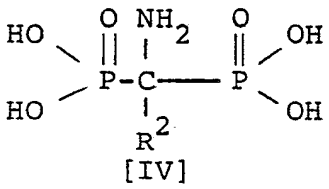
in which $R^1$ and X are each as defined above.

The object compound [I] or its salt can be prepared by processes as illustrated in the following reaction schemes.

Process 1

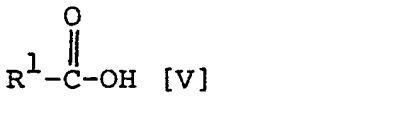


Process 2



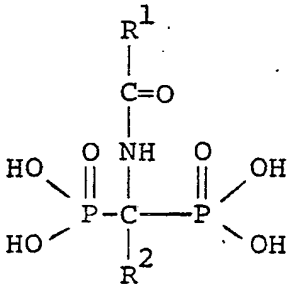
[IV]

or its reactive derivative at the amino group or its salt



[V]

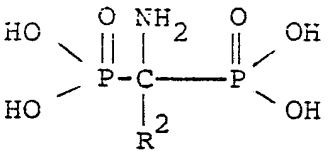
or its reactive derivative at the carboxy group or its salt



[Ib]

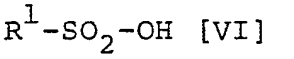
or its salt

Process 3



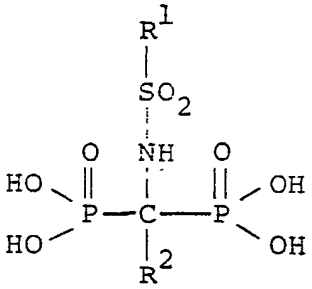
[IV]

or its reactive derivative at the amino group or its salt



[VI]

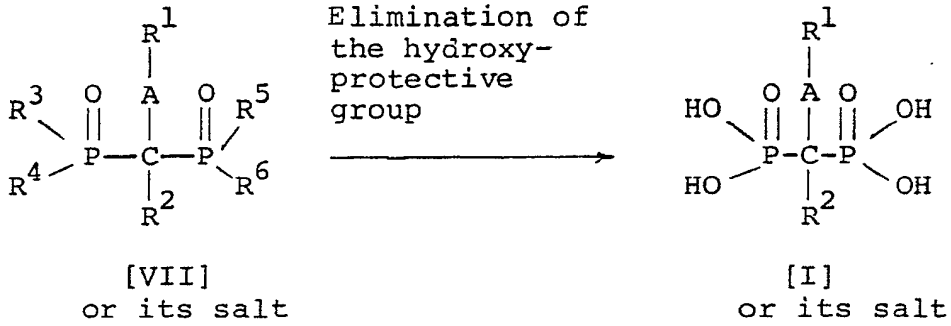
or its reactive derivative at the sulfo group or its salt



[Ic]

or its salt

Process 4




[VII] or its salt

[I] or its salt

wherein

$R^3$, $R^4$, $R^5$ and $R^6$ are each protected hydroxy, and

$R^1$, $R^2$, A and X are each as defined above.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "aryl" may be phenyl, naphthyl, tolyl, mesityl, cumenyl, and the like, preferably phenyl, naphthyl and $C_1$-$C_6$ alkyl [e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, etc.] substituted phenyl.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic one containing at least one hetero atom such as nitrogen atom, oxygen atom or sulfur atom.

The preferred examples of thus defined "heterocyclic group" may be unsaturated, 3 to 8-membered, more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyridyl N-oxide, dihydropyridyl, tetrahydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, triazolyl, tetrazinyl, tetrazolyl, etc.;

unsaturated, condensed heterocyclic group containing I to 5 nitrogen atom(s), for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing I to 2 oxygen atom(s) and I to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl, etc.;

saturated, 3 to 8-membered heteromonocyclic group containing I to 2 oxygen atom(s) and I to 3 nitrogen atom(s), for example, morpholino, sydnonyl, etc.;

unsaturated, condensed heterocyclic group containing I to 2 oxygen atom(s) and I to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing I to 2 sulfur atom(s) and I to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing I to 2 sulfur atom(s), for example, thienyl, etc.;

unsaturated, condensed heterocyclic group containing I to 2 sulfur atom(s) and I to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated, 3 to 8-membered heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated, condensed heterocyclic group containing I to 2 sulfur atom(s), for example, benzothienyl, etc.;

unsaturated, condensed heterocyclic group containing I to 2 oxygen atom(s), for example, benzofuranyl, etc.; or the like.

The above-mentioned "aryl" and "heterocyclic group" may be substituted with one or more, preferably one to three, more preferably one or two substituent(s) selected from the group consisting of the aforesaid $C_1$-$C_6$ alkyl; $C_1$-$C_6$ alkoxy [e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, pentyloxy, hexyloxy, etc.]; $C_1$-$C_6$ alkylthio[e.g. methylthio, ethylthio, propylthio, isopropylthio, butylthio, pentylthio, hexylthio, etc.]; halo-($C_1$-$C_6$)alkyl, preferably mono-, di- or tri(halo)-$C_1$-$C_6$ alkyl [e.g. chloromethyl, bromomethyl, fluoromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 2-bromoethyl, 3-chloropropyl, etc.]; acyl such as $C_1$-$C_6$ alkanoyl [e.g. formyl, acetyl, propionyl, hexanoyl, pivaloyl, etc.], $C_1$-$C_6$ alkoxycarbonyl [e.g. methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl, etc.], ar-

($C_1$-$C_6$)alkoxycarbonyl [e.g. benzyloxycarbonyl, etc.], $C_1$-$C_6$ alkylsulfonyl [e.g. mesyl, ethylsulfonyl, etc.], arylsulfonyl [e.g. phenylsulfonyl, tosyl, etc.], or the like; acylamino such as $C_1$-$C_6$ alkanoylamino [e.g. formylamino, acetylamino, propionylamino, etc.], $C_1$-$C_6$ alkylsulfonylamino [e.g. mesylamino, ethylsulfonylamino, propylsulfonylamino, etc.] or the like; and halogen [e.g. fluoro, chloro, bromo, iodo, etc.].

Preferable example of "aryl or a heterocyclic group, each of which may be substituted with substituent(s) selected from the group consisting of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkylthio, halo($C_1$-$C_6$)alkyl, acyl, acylamino and halogen" thus defined may be phenyl, naphthyl, mono or di or tri($C_1$-$C_6$)alkylphenyl [e.g. tolyl, ethylphenyl, propylphenyl, cumenyl, butylphenyl, xylyl, mesityl, etc.], mono or di or tri($C_1$-$C_6$)alkoxyphenyl [e.g. methoxyphenyl, ethoxyphenyl, propoxyphenyl, isopropoxyphenyl, butoxyphenyl, neopentyloxyphenyl, dimethoxyphenyl, etc.], mono or di or tri($C_1$-$C_6$)alkylthiophenyl [e.g. methylthiophenyl, ethylthiophenyl, propylthiophenyl, isopropylthiophenyl, butylthiophenyl, dimethylthiophenyl, etc.], mono or di or trihalophenyl [e.g. fluorophenyl, chlorophenyl, bromophenyl, iodophenyl, dichlorophenyl, (fluoro)chlorophenyl, diiodophenyl, difluorophenyl, trifluorophenyl, trichlorophenyl, etc.], mono or di or tri[halo($C_1$-$C_6$)alkyl]phenyl [e.g. chloromethylphenyl, dichloromethylphenyl, trifluoromethylphenyl, di(trifluoromethyl)phenyl, etc.], mono or di or triacylaminophenyl [e.g. mono or di or tri($C_1$-$C_6$)alkanoylaminophenyl (e.g. formylaminophenyl, acetylaminophenyl, propionylaminophenyl, di(acetylamino)phenyl, etc.), mono or di or tri($C_1$-$C_6$)alkylsulfonylaminophenyl (e.g. mesylaminophenyl, ethylsulfonylaminophenyl, propylsulfonylaminophenyl, di(mesylamino)phenyl, etc.), etc.], halogen and halo($C_1$-$C_6$)alkyl substituted phenyl [e.g. (chloro)trifluoromethylphenyl, (fluoro)trifluoromethylphenyl, di(chloro)chloromethylphenyl, etc.], $C_1$-$C_6$ alkoxy and halo($C_1$-$C_6$)alkyl substituted phenyl [e.g. (methoxy)trifluoromethylphenyl, (ethoxy)trifluoromethylphenyl, di(methoxy)chloromethylphenyl, etc.], pyridyl, mono or di or tri($C_1$-$C_6$)alkylpyridyl [e.g. methylpyridyl, ethylpyridyl, propylpyridyl, dimethylpyridyl, etc.], imidazolyl, imidazolyl substituted with acyl such as $C_1$-$C_6$ alkoxycarbonyl substituted imidazolyl [e.g. tert-butoxycarbonylimidazolyl, etc.] or the like, thienyl, quinolyl, benzo[b]thienyl, benzothiazolyl and mono or di or trihalobenzothiazolyl [e.g. chlorobenzothiazolyl, fluorobenzothiazolyl, etc.], in which more preferable one may be phenyl, mono($C_1$-$C_4$)alkylphenyl, mono ($C_1$-$C_4$) alkoxyphenyl, mono($C_1$-$C_4$)alkylthiophenyl, mono or dihalophenyl, mono[halo($C_1$-$C_4$)alkyl]phenyl, mono($C_1$-$C_4$)alkanoylaminophenyl, mono($C_1$-$C_4$)alkylsulfonylaminophenyl, halogen and halo($C_1$-$C_4$)alkyl substituted phenyl, $C_1$-$C_4$ alkoxy and halo($C_1$-$C_4$)alkyl substituted phenyl, pyridyl, mono($C_1$-$C_4$)alkylpyridyl, imidazolyl, $C_1$-$C_4$ alkoxycarbonylimidazolyl, thienyl, quinolyl, benzo[b]thienyl, benzothiazolyl and mono-halobenzothiazolyl, and most preferable ones are phenyl, tolyl, naphthyl, methoxyphenyl, methylthiophenyl, chlorophenyl, fluorophenyl, dichlorophenyl, trifluoromethylphenyl, acetylaminophenyl, mesylaminophenyl, (chloro)trifluoromethylphenyl, (methoxy)trifluoromethylphenyl, pyridyl, methylpyridyl, imidazolyl, tert-butoxycarbonylimidazolyl, thienyl, quinolyl, benzo[b]thienyl, benzothiazolyl and chlorobenzothiazolyl.

Suitable "$C_1$-$C_6$ alkyl" may be a straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which more preferable one may be $C_1$-$C_4$ alkyl and the most preferable ones are methyl and butyl.

"$C_1$-$C_6$ alkyl" group for $R^1$ may be substituted with the above-mentioned heterocyclic group which may be substituted with the above-mentioned acyl.

Suitable "protected hydroxy" may be hydroxy group protected by conventional protective group such as $C_1$-$C_6$ alkoxy [e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, sec-butoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy, hexyloxy, etc.], optionally substituted ar($C_1$-$C_6$)alkoxy, for example, mono or di or triphenyl($C_1$-$C_6$)alkoxy which may be substituted with nitro [e.g. benzyloxy, 4-nitrobenzyloxy, benzhydryloxy, trityloxy, etc.], or the like, in which the preferable example may be $C_1$-$C_6$ alkoxy, more preferable one may be $C_1$-$C_4$ alkoxy and the most preferable ones are ethoxy and isopropoxy.

Suitable pharmaceutically acceptable salts of the object compounds [I] are conventional non-toxic salts and include an inorganic base salt such as an alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.] or an ammonium salt; an organic base salt such as an organic amine salt [e.g. methylamine salt, ethylamine salt, propylamine salt, isopropylamine salt, butylamine salt, tert-butylamine salt, dimethylamine salt, diethylamine salt, trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.], an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], a salt with an amino acid [e.g. arginine salt, aspartic acid salt, glutamic acid salt, etc.], or the like.

In this respect, it is to be noted the compounds [Ia] to [Ic] are included within the scope of the compounds [I], and accordingly the suitable salts of these compounds [Ia] to [Ic] are to be referred to those as exemplified for the object compounds [I] mentioned above.

The processes for preparing the object compounds [I] of the present invention are explained in detail in

the following.

Process 1

The object compound [Ia] or its salt can be prepared by reacting a compound [II] or its salt with a compound [III] or its equivalent or a salt thereof.

Suitable salts of the compound [II] can be referred to the base salts as exemplified for the compound [I].

Suitable salts of the compound [III] can be referred to the acid addition salts as exemplified for the compound [I].

Suitable examples of equivalent of the compound [III] may include intermolecular condensed compounds of the compound [III] such as 3-(2-pyridyl)-3,4-dihydro-2H-pyrido[1,2-a]-1,3,5-triazine-2,4-dione prepared by subjecting 2-pyridylisothiocyanate to intermolecular condensation, etc.

This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, chloroform, methylene chloride, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction.

Further, this reaction can be carried out in the presence of a base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydride or hydroxide thereof, alkali metal alkoxide [e.g. sodium methoxide, sodium ethoxide, potassium tert-butoxide, etc.], or the like.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process 2

The object compound [Ib] or its salt can be prepared by reacting a compound [IV] or its reactive derivative at the amino group or its salt with a compound [V] or its reactive derivative at the carboxy group or its salt.

Suitable reactive derivative at the amino group of the compound [IV] may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound [IV] with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound [IV] with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis-(trimethylsilyl)urea or the like; a derivative formed by reaction of the compound [IV] with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound [IV] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

Suitable reactive derivative at the carboxy group of the compound [V] may include an acid halide, an acid anhydride, an activated amide, an activated ester, and the like. Suitable examples of the reactive derivatives may be an acid chloride; an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid, etc.], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid, etc.] or aromatic carboxylic acid [e.g. benzoic acid, etc.]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH$-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole, etc.], and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound [V] to be used.

Suitable salts of the compound [V] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

In this reaction, when the compound [V] is used in a free acid form or its salt form, the reaction is

preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; l-alkoxy-l-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphoshate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)-isoxazolium hydroxide intramolecular salt; l-(p-chlorobenzenesulfonyloxy)-6-chloro-lH-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metel bicarbonate, tri(lower)alkylamine, pyridine, di(lower)alkylaminopyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine, or the like. A liquid base can also be used as a solvent.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 3

The object compound [Ic] or its salt can be prepared by reacting a compound [IV] or its reactive derivative at the amino group or its salt with a compound [VI] or its reactive derivative at the sulfo group or its salt.

Suitable salts of the compound [VI] and its reactive derivative can be referred to the salts as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction conditions [e.g. base, reactive derivative, condensing agent, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 2.

Process 4

The object compound [I] or its salt can be prepared by subjecting a compound [VII] or its salt to elimination reaction of the hydroxy-protective group.

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

Suitable salts of the compound [VII] can be referred to the ones as exemplified for the compound [I].

The hydrolysis is preferably carried out in the presence of a base, an acid including Lewis acid, or halosilane compound.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], an alkaline earth metal [e.g. magnesium, calcium, etc.], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, l,5-diazabicyclo[4.3.0]-non-5-ene, l,4-diazabicyclo[2.2.2]octane, l,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

Suitable halosilane compound may include halotri(lower)alkylsilane [e.g. iodotrimethylsilane, bromotrimethylsilane, etc.], and the like.

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, chloroform, tetrachloromethane, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction.

A liquid base, acid or halosilane compound can also be used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid,

hydrochloric acid, hydrobromic acid, etc.].

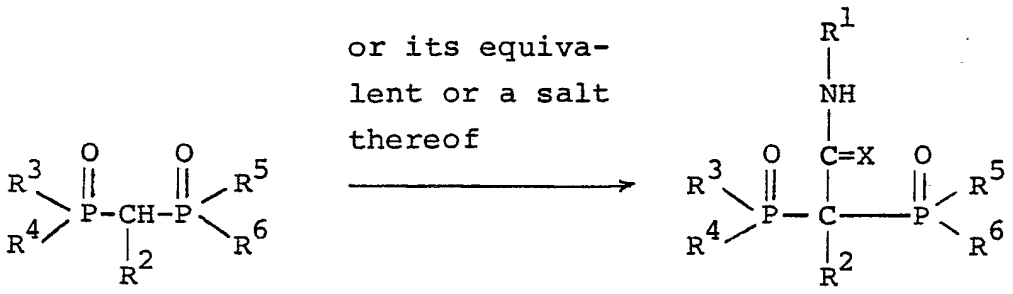
Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.], palladium catalysts [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.], nickel catalysts [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], cobalt catalysts [e.g. reduced cobalt, Raney cobalt, etc.], iron catalysts [e.g. reduced iron, Raney iron, etc.], copper catalysts [e.g. reduced copper, Raney copper, Ullman copper, etc.] and the like.

The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the abovementioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the abovementioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, etc., or a mixture thereof.

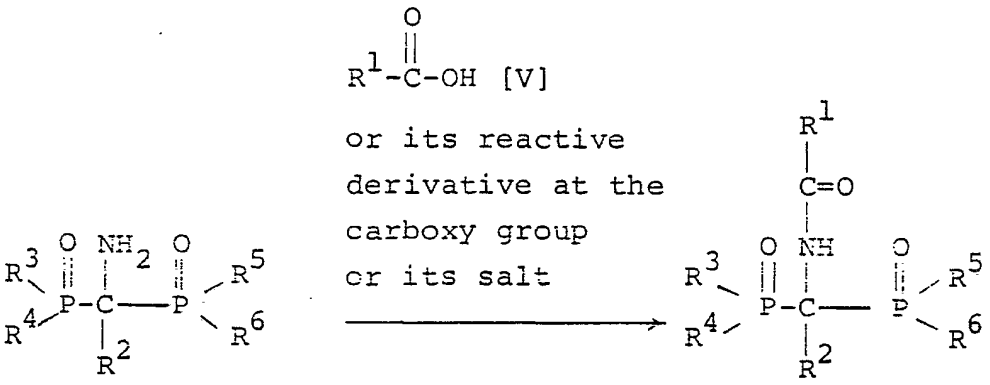
The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to heating.

The starting compound [VII], some of which are new, or its salt can be prepared by processes as illustrated in the following reaction schemes.

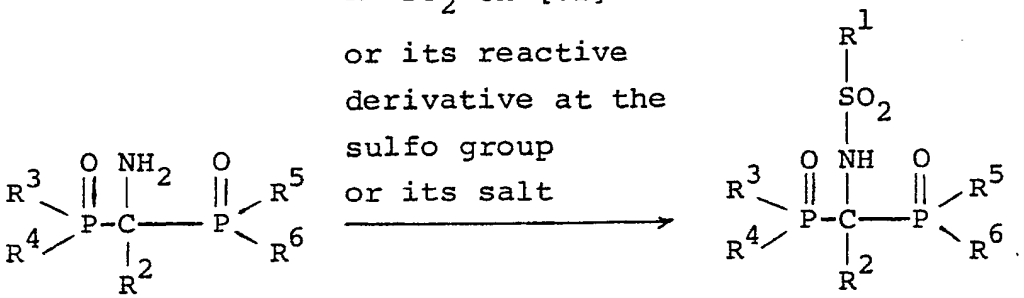
Process A




Process B



Process C



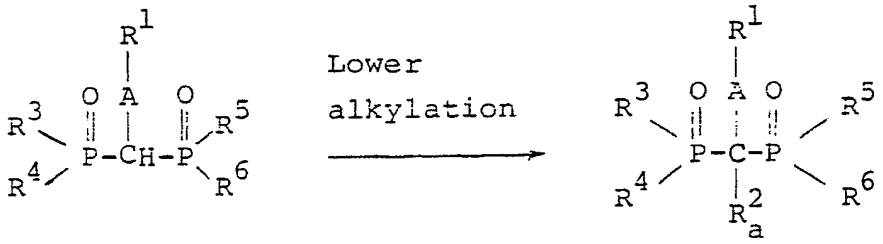

[IX]

or its reactive derivative at the amino group or its salt

[VIIc]

or its salt

Process D




[VIId]

or its salt

[VIIe]

or its salt

wherein $R^2_a$ is lower alkyl, and $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, A and X are each as defined above.

The above-mentioned processes for preparing the starting compounds are explained in detail in the following.

Process A

The compound [VIIa] or its salt can be prepared by reacting a compound [VIII] or its salt with a compound [III] or its equivalent or a salt thereof.

Suitable salts of the compound [VIII] can be referred to the base salts as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process I, and therefore the reaction mode and reaction conditions [e.g. base, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process I.

Process B

The compound [VIIb] or its salt can be prepared by reacting a compound [IX] or its reactive derivative at the amino group or its salt with a compound [V] or its reactive derivative at the carboxy group or its salt.

Suitable salts of the compound [IX] and its reactive derivative can be referred to the ones as exemplified for the compound [I].

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction conditions [e.g. reactive derivative, condensing agent, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 2.

Process C

The compound [VIIc] or its salt can be prepared by reacting a compound [IX] or its reactive derivative at the amino group or its salt with a compound [VI] or its reactive derivative at the sulfo group or its salt.

This reaction can be carried out in substantially the same manner as Process 2, and therefore the reaction mode and reaction conditions [e.g. base, reactive derivative, condensing agent, solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 2.

Process D

The compound [VIIe] or its salt can be prepared by reacting a compound [VIId] or its salt with a lower alkylating agent.

Suitable salts of the compound [VIId] can be referred to the ones as exemplified for the compound [I].

Suitable salts of the compound [VIIe] can be referred to the acid addition salt as exemplified for the compound [I].

Suitable lower alkylating agents may be lower alkyl halide [e.g. methyl iodide, ethyl iodide, propyl iodide, butyl iodide, etc.], lower alkyl arenesulfonate [e.g. methyl benzenesulfonate, ethyl tosylate, etc.], di-(lower)alkyl sulfate [e.g. dimethyl sulfate, diethyl sulfate, etc.] or the like.

This reaction can be carried out in the presence of a base as exemplified in Process I.

This reaction is usually carried out in a solvent such as dioxane, tetrahydrofuran, benzene, chloroform, methylene chloride, N;N-dimethylformamide or any other organic solvent which does not adversely influence the reaction, and in case that the above-mentioned lower alkylating agent is liquid, it can also be used as a solvent.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

Both reactions of Process A and Process D can be carried out simultaneously, where a compound [III] and a lower alkylating agent are added to a compound [VIII] wherein $R^2$ is hydrogen to give a compound [VIIe]. This process is also included within the scope of the present invention.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound [I] and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

The object compounds [I] and pharmaceutically acceptable salts thereof possess strong inhibitory activities on bone resorption, and useful for therapeutical treatment of bone diseases characterized by abnormal bone metabolism such as osteoporosis, Paget's bone disease, osteolysis, hypercalcemia of malignancy and rheumatoid arthritis.

For therapeutic purpose, the compounds [I] and pharmaceutically acceptable salts thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, solution, suspension, emulsion, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of the compounds [I] will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound [I] may be effective for treating said bone diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

In order to illustrate the usefulness of the object compound [I], the pharmacological test data of some

representative compounds of the compound [I] are shown in the following.

Test method :

Neonatal calvaria were dissected aseptically from 1-2 day old rat (Wistar), washed in Dulbecco's modified eagle's medium and divided along the sagittal suture. The calvaria halves were pooled and randomized in the different groups. The calvaria halves were cultured separately as free-floating bones in multi-well dishes containing a 2 ml of Dulbecco's modified eagle's medium, with 10% heat-inactivated (56 ° C for 1 hr) fetal calf serum. Treatment of hPTH(1-34)($1\times10^{-8}$M) and the Test Compound ($1\times10^{-7}$ or $1\times10^{-6}$M) was begun at zero time. All incubations were performed at 37 ° C, under an atmosphere of 95% air and 5% $CO_2$ for 6 days. Bone resporption was determined by measuring the accumulation of calcium in the medium at 6 days. The concentration of total calcium in culture medium was measured by OCPC method with a spectrophotometer (Hitachi model U-3200, Tokyo, Japan).

As comparative data, similar tests were conducted using culture medium with hPTH ($1\times10^{-8}$M) only, and culture medium without both hPTH and Test Compound.

Test results were represented in terms of percentage of inhibition calculated by the following formula :

$$\text{Inhibition (\%)} = \frac{C_P - C_D}{C_P - C_O} \times 100$$

CD : the concentration of total calcium in culture medium treated with both hPTH and Test Compound

CO : the concentration of total calcium in control culture medium without both hPTH and Test Compound

CP : the concentration of total calcium in culture medium treated with hPTH only

Test compounds :

(a) Tris(tert-butylamine)salt of [N-(phenyl)thiocarbamoylmethylene]bis(phosphonic acid)
(b) Tris(tert-butylamine)salt of [N-(4-chlorophenyl)carbamoylmethylene]bis(phosphonic acid)
(c) Tris(tert-butylamine)salt of [N-(4-chlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
(d) Disodium salt of [N-(2-benzo[b]thienyl)thiocarbamoylmethylene]bis(phosphonic acid)
(e) Disodium salt of [N-(4-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
(f) Disodium salt of [N-(3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
(g) Disodium salt of [N-(4-chloro-3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
(h) Disodium salt of [N-(4-methoxy-3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
(i) Bis(tert-butylamine)salt of [(2-benzo[b]thiophenecarboxamido)methylene]bis(phosphonic acid)
(j) Tris(tert-butylamine)salt of [(2-quinolinecarboxamido)methylene]bis(phosphonic acid)
(k) Disodium salt of [(4-chlorophenyl)sulfonylaminomethylene]bis(phosphonic acid)
(ℓ) Disodium salt of [N-(3-mesylaminophenyl)thiocarbamoylmethylene]bis(phosphonic acid)

Test Results

| Test Compounds | Dose (M) | Inhibition (%) |
|---|---|---|
| (a) | $1 \times 10^{-7}$ | 54.3 |
| | $1 \times 10^{-6}$ | 66.3 |
| (b) | $1 \times 10^{-7}$ | 46.6 |
| | $1 \times 10^{-6}$ | 56.9 |
| (c) | $1 \times 10^{-6}$ | 57.0 |
| (d) | $1 \times 10^{-6}$ | 59.7 |
| (e) | $1 \times 10^{-6}$ | 65.9 |
| (f) | $1 \times 10^{-6}$ | 68.9 |
| (g) | $1 \times 10^{-6}$ | 112.4 |
| (h) | $1 \times 10^{-6}$ | 77.7 |
| (i) | $1 \times 10^{-7}$ | 45.0 |
| (j) | $1 \times 10^{-7}$ | 46.9 |
| | $1 \times 10^{-6}$ | 53.8 |
| (k) | $1 \times 10^{-6}$ | 71.0 |
| (ℓ) | $1 \times 10^{-6}$ | 52.4 |

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation I

To a stirred solution of 2-aminobenzo[b]thiophene (1.11 g) in anhydrous toluene (4.5 ml) was added carbon disulfide (0.62 g) and triethylamine (0.755 g) successively. The solution was then stirred at 0-5°C for 3 days under nitrogen gas atmosphere. The precipitate was collected by filtration and was washed with anhydrous toluene (10 ml). The obtained white powder was dissolved in chloroform (4.5 ml), treated with triethylamine (0.76 g), and cooled to 0°C. To this solution was added dropwise ethyl chloroformate (0.84 g) over a period of 20 minutes. After being stirred at ambient temperature for one hour, the solution was washed twice with 1N hydrochloric acid (5 ml), and brine, and dried. The solvent was evaporated under reduced pressure and the residue was subjected to column chromatography on silica gel, eluted with n-hexane to give benzo[b]thiophene-2-isothiocyanate (118 mg) as an oil.
IR (Neat) : 2080 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 7.06 (1H, s), 7.32-7.41 (2H, m), 7.63-7.73 (2H, m)

Preparation 2

To a suspension of sodium hydride (120 mg, 60% oil dispersion) in distilled tetrahydrofuran (4 ml) was added tetraisopropyl methylenebis(phosphonate)(688 mg) in one portion at ambient temperature. After stirring for a few minutes, the mixture was allowed to cool in an ice bath and phenyl isothiocyanate (0.36 ml) was added thereto. The reaction mixture was stirred for 3 hours at ambient temperature and methanol (2 ml) was added to the reaction mixture to quench excess phenyl isothiocyanate. The mixture was concentrated under reduced pressure. The residue was dissolved in a mixture of diethyl ether and 1N hydrochloric acid. The separated organic layer was washed with water and dried over magnesium sulfate. The solvent was removed and the residue was subjected to column chromatography on silica gel using a mixture of chloroform and methanol (30:1 V/V) as an eluent to give tetraisopropyl [N-(phenyl)-thiocarbamoylmethylene]bis(phosphonate) (0.75 g) as a crystal.

mp : 64-66° C
IR (Nujol) : 3300, 1600, 1500, 1400, 1250, 1000 $cm^{-1}$
NMR ($CDCl_3$, δ) : 1.2-1.6 (24H, m), 4.31 (1H, t, J = 23.5Hz), 4.65-5.0 (4H, m), 7.2-7.45 (3H, m), 7.75-7.85 (2H, m), 10.24 (1H, br s)

The following compounds (Preparations 3 to 27) were obtained according to a similar manner to that of Preparation 2.

Preparation 3
Tetraisopropyl [N-(4-fluorophenyl)carbamoylmethylene]bis(phosphonate)
mp : 173-174° C
IR (Nujol) : 3450, 3350, 1665 $cm^{-1}$
NMR ($CDCl_3$, δ) : 1.26-1.50 (24H, m), 3.62 (1H, t, J = 20Hz), 4.69-4.97 (4H, m), 7.00 (2H, t, J = 8Hz), 7.48 (2H, dd, J = 8 and 5Hz), 7.56 (1H, s)

Preparation 4
Tetraisopropyl [N-(p-tolyl)carbamoylmethylene]bis(phosphonate)
mp : 96-98° C
IR (Nujol) : 3300, 1660 $cm^{-1}$
NMR ($CDCl_3$, δ) : 1.20-1.52 (24H, m), 2.32 (3H, s), 3.53 (1H, t, J = 20Hz), 4.70-4.92 (4H, m), 7.12 (2H, d, J = 8Hz), 7.42 (2H, d, J = 8Hz), 8.69 (1H, s)

Preparation 5
Tetraisopropyl [N-(4-methoxyphenyl)carbamoylmethylene]bis(phosphonate)
mp : 99-100° C
IR (Nujol) : 3300, 1660 $cm^{-1}$
NMR ($CDCl_3$, δ) : .31-1.41 (24H, m), 3.53 (1H, t, J = 23Hz), 3.79 (3H, s), 4.71-4.92 (4H, m), 6.86 (2H, d, J = 9Hz), 7.44 (2H, d, J = 9Hz), 8.65 (1H, s)

Preparation 6
Tetraisopropyl [N-(4-chlorophenyl)thiocarbamoylmethylene]bis(phosphonate)
NMR ($CDCl_3$, δ) : 1.21-1.46 (24H, m), 4.30 (1H, t, J = 22Hz), 4.78 (4H, m), 7.35 and 7.78 (4H, ABq, J = 8.8Hz), 10.25 (1H, br s)

Preparation 7
Tetraisopropyl [N-(1-naphthyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3500, 3320, 2975, 2925, 1590, 1380, 1250, 1000 $cm^{-1}$
NMR ($CDCl_3$, δ) : 1.37-1.47 (24H, m), 4.51 (1H, t, J = 24Hz), 4.90 (4H, m), 7.48-8.34 (7H, m), 10.30 (1H, br s)

Preparation 8
Tetraisopropyl [N-(3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonate)
mp : 49-51° C
IR ($CH_2Cl_2$ : 2980, 2930, 1450, 1385, 1335, 1130, 990 $cm^{-1}$
NMR ($CDCl_3$, δ) : 1.25-1.57 (24H, m), 4.34 (1H, t, J = 23Hz), 4.70-5.00 (4H, m), 7.50-7.60 (2H, m), 8.04 (1H, m), 8.16 (1H, s), 10.4 (1H, s)

Preparation 9
Tetraisopropyl [N-(4-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonate)
mp : 98-100° C
IR (Nujol) : 3250, 3200, 1610, 1320, 1250, 1120 $cm^{-1}$
NMR ($CDCl_3$, δ) : 1.31-1.44 (24H, m), 4.32 (1H, t, J = 23Hz), 4.81 (4H, m), 7.66 and 8.00 (4H, ABq, J = 8.5Hz), 10.43 (1H, s)

Preparation 10
Tetraisopropyl [N-(3-chlorophenyl)thiocarbamoylmethylene]bis(phosphonate) mp : 61-62° C
IR (Neat) : 3450, 3300, 1595, 1550, 1480, 1380, 1260, 1100, 1000 $cm^{-1}$
NMR ($CDCl_3$, δ) : 1.21-1.44 (24H, m), 4.30 (1H, t, J = 23Hz), 4.69-4.91 (4H, m), 7.20-7.37 (2H, m), 7.65 (1H, br d, J = 8Hz), 8.00 (1H, br s), 10.27 (1H, s)

Preparation 11
Tetraisopropyl [N-(2-chlorophenyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3500, 3300, 1380, 1260, 990 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.28-1.43 (24H, m), 4.26 (1H, t, J = 20Hz), 4.76-4.95 (4H, m), 7.17-7.36 (2H, m), 7.76 (1H, dd, J = 8 and 2Hz), 8.45 (1H, dd, J = 8 and 2Hz), 10.20 (1H, s)

Preparation 12
Tetraisopropyl [N-(4-fluorophenyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3480, 3300, 1510, 1000 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.26-1.53 (24H, m), 4.32 (1H, t, J = 24Hz), 4.70-4.94 (4H, m), 7.04-7.13 (2H, m), 7.71-7.78 (2H, m), 10.19 (1H, s)

Preparation 13
Tetraisopropyl [N-(p-tolyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3500, 3300, 1535, 1385, 1260, 1000 $cm^{-1}$
MR ($CDCl_3$, $\delta$) : .21-1.43 (24H, m), 2.35 (3H, s), 4.31 (1H, t, J = 20Hz), 4.70-4.94 (4H, m), 7.20 (2H, d, J = 8Hz), 7.65 (2H, d, J = 8Hz), 10.16 (1H, s)

Preparation 14
Tetraisopropyl [N-(2-methoxyphenyl)thiocarbamoylmethylene]bis(phosphonate)
NMR ($CDCl_3$, $\delta$) : 18-1.50 (24H, m), 3.92 (3H, m), 4.37 (1H, t, J = 24Hz), 4.73-4.93 (4H, m), 6.94-7.03 (2H, m), 7.16 (1H, td, J = 8 and 2Hz), 8.96 (1H, d, J = 8Hz), 10.45 (1H, s)

Preparation 15
Tetraisopropyl [N-(3,4-dichlorophenyl)thiocarbamoylmethylene]bis(phosphonate)
mp : 90-92° C
IR (Nujol) : 3300, 3200, 1260, 990 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.32-1.71 (24H, m), 4.29 (1H, t, J = 23Hz), 4.67-4.94 (4H, m), 7.45 (1H, d, J = 9Hz), 7.65 (1H, dd, J = 9 and 2Hz), 8.14 (1H, d, J = 2Hz), 10.30 (1H, s)

Preparation 16
Tetraisopropyl [N-(2-benzo[b]thienyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3500, 3210, 1600, 1580, 1380, 1260, 1100, 1000 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.23-1.44 (24H, m), 4.31 (1H, t, J = 22Hz), 4.66-4.94 (4H, m), 7.26-7.40 (3H, m), 7.66-7.80 (2H, m), 11.11 (1H, s)

Preparation 17
Tetraisopropyl [N-(2-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3330, 2980, 1530, 1460, 1380, 1320, 1260, 1170, 1140, 1100 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.20-1.50 (24H, m), 4.48 (1H, t, J = 23Hz), 4.70-5.00 (4H, m), 7.41 (1H, t, J = 8Hz), 7.60 (1H, t, J = 8Hz), 7.72 (1H, d, J = 8Hz), 7.87 (1H, d, J = 8Hz), 9.91 (1H, s)

Preparation 18
Tetraisopropyl [N-(4-chloro-3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonate)
mp : 101-102° C
IR (Nujol) : 3150, 3100, 1390, 1320, 1210, 1000 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.25-1.46 (24H, m), 4.33 (1H, t, J = 22Hz), 4.74-4.97 (4H, m), 7.54 (1H, d, J = 8Hz), 8.05 (1H, dd, J = 8 and 3Hz), 8.22 (1H, d, J = 3Hz), 10.41 (1H, s)

Preparation 19
Tetraisopropyl [N-(4-methoxy-3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3450, 3250, 1500, 1260, 1140 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.34-1.44 (24H, m), 3.92 (3H, s), 4.32 (1H, t, J = 23Hz), 4.70-4.94 (4H, m), 7.02 (1H, d, J = 8Hz), 7.93 (1H, br s), 7.95 (1H, dd, J = 8 and 2Hz)

Preparation 20
Tetraisopropyl [N-(4-trifluoromethylphenyl)carbamoylmethylene]bis(phosphonate)
mp : 136-137° C

IR (Nujol) : 3250, 3200, 1670, 1600, 1540, 1320, 1250, 1120, 950 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.30-1.42 (24H, m), 3.58 (1H, t, J = 22Hz), 4.73-4.91 (4H, m), 7.57 and 7.66 (each 2H, d, J = 7Hz), 9.05 (1H, s)

Preparation 21
Tetraisopropyl (N-methylcarbamoylmethylene)bis(phosphonate)
mp : 96-100 °C
IR (Nujol) : 3270, 1640, 1255, 980 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.2-1.5 (24H, m), 2.85 (3H, d, J = 4Hz), 3.48 (1H, t, J = 23Hz), 4.65-4.95 (4H, m), 6.86 (1H, br)

Preparation 22
Tetraisopropyl [N-(n-butyl)thiocarbamoylmethylene]bis(phosphonate)
IR (neat) : 3500, 3350, 1545, 1385, 1260 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 0.95 (3H, t, J = 7Hz), 1.21-1.54 (26H, m), 1.59-1.74 (2H, m), 3.64 (2H, dt, J = 7Hz), 4.23 (1H, t, J = 23Hz), 4.65-4.89 (4H, m), 8.56 (1H, br m)

Preparation 23
Tetraisopropyl [N-(4-methylthiophenyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Nujol) : 1480, 1450, 1090, 920, 810 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.15-1.5 (24H, m), 2.47 (1H, s), 4.27 (1H, t, J = 21Hz), 4.5-4.95 (4H, m), 7.26 (2H, d, J = 8.6Hz), 7.76 (2H, d, J = 8.6Hz), 10.2 (1H, s)

Preparation 24
Tetraisopropyl [N-(4-mesylaminophenyl)thiocarbamoylmethylene]bis(phosphonate)
mp : 141-143 °C
IR (Nujol) : 3300, 3100, 1610, 1510, 1420, 1380, 1335, 1250, 1150, 1000 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.33-1.67 (24H, m), 3.02 (3H, s), 4.30 (1H, t, J = 23Hz), 4.70-4.92 (4H, m), 7.29 and 7.50 (each 2H, d, J = 9Hz), 7.45 (1H, s), 10.23 (1H, s)

Preparation 25
Tetraisopropyl [N-(3-mesylaminophenyl)thiocarbamoylmethylene]bis(phosphonate)
mp : 144-145 °C
IR (Neat) : 3450, 3150, 1600, 1380, 1240, 1150 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.34-1.48 (24H, m), 3.06 (3H, s), 4.31 (1H, t, J = 22Hz), 4.73-4.91 (4H, m), 6.84 (1H, br s), 7.12 (1H, br d, J = 6Hz), 7.32-7.39 (2H, m), 7.98 (1H, br s), 10.29 (1H, br s)

Preparation 26
Tetraisopropyl [N-(4-acetylaminophenyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3500, 3300, 1690, 1515, 1385, 1260, 1100 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.13-1.65 (24H, m), 2.21 (3H, s), 4.34 (1H, t, J = 22Hz), 4.58-4.98 (4H, m), 7.55 and 7.76 (2H, d, J = 7Hz), 10.20 (1H, s)

Preparation 27
Tetraisopropyl [N-(3-acetylaminophenyl)thiocarbamoylmethylene]bis(phosphonate)
IR (Neat) : 3450, 3300, 1690, 1610, 1550, 1260, 1110 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.10-1.62 (24H, m), 2.17 (3H, s), 4.30 (1H, t, J = 22Hz), 4.55-5.00 (4H, m), 7.30-7.62 (3H, m), 8.15 (1H, s)

Preparation 28

A mixture of tetraisopropyl methylenebis(phosphonate) (668 mg) and potassium tert-butoxide (224 mg) in anhydrous toluene (5 ml) was refluxed for 1 hour. After cooling to ambient temperature, 3-(2-pyridyl)-3,4-dihydro-2H-pyrido[1,2-a]-1,3,5-triazin-2,4-dione (2.0 g) and anhydrous tetrahydrofuran (25 ml) were added to the solution, and the mixture was stirred at 60 °C for 30 minutes. The reaction mixture was cooled in an ice-water bath and then quenched with 1N hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried, and evaporated in vacuo. The residue was subjected to column chromatography on silica gel eluted with methanol-methylene chloride-diethyl ether (1:10:30 V/V) to give tetraisopropyl [N-(2-pyridyl)-

carbamoylmethylene]bis(phosphonate)(1.42 g) as an oil.
IR (Neat) : 3360, 3250, 1690 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.20-1.58 (24H, m), 2.30 (1H, br s), 3.60 (1H, t, J=20Hz), 4.67-5.05 (4H, m), 7.06 (1H, dd, J=7 and 5Hz), 7.60-7.77 (1H, m), 8.12 (1H, d, J=7Hz), 8.30 (1H, br d, J=5Hz), 9.11 (1H, br s)

Preparation 29

To a solution of 2-benzo[b]thiophenecarbonyl chloride prepared from 2-benzo[b]thiophenecarboxylic acid (356 mg) and oxalyl chloride (0.35 ml) in methylene chloride (2 ml) was added dropwise a mixture of tetraethyl (aminomethylene)bis(phosphonate) (606 mg), pyridine (316 mg) and trace amounts of 4-(dimethylamino)pyridine in methylene chloride (8 ml) at 5° C. The mixture was stirred for 2 hours at ambient temperature followed by the addition of ethyl acetate. The mixture was washed with water, 1N hydrochloric acid, saturated aqueous solution of sodium bicarbonate and brine successively. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was treated with diisopropyl ether to give tetraethyl [(2-benzo[b]thiophenecarboxamido)methylene]bis(phosphonate) (790 mg) as a white powder which was recrystallized from a mixture of ethyl acetate and n-hexane.
mp : 120-121° C
IR (Nujol) : 3210, 1640, 1630 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.30-1.42 (12H, m), 4.09-4.41 (8H, m), 5.22 (1H, td, J=20 and 9Hz), 6.63 (1H, d, J=9Hz), 7.38-7.50 (2H, m), 7.85 (1H, s), 7.85-7.92 (2H, m)

The following compounds (Preparations 30 to 33) were obtained according to a similar manner to that of Preparation 29.

Preparation 30
Tetraethyl [(2-quinolinecarboxamido)methylene]bis(phosphonate)
mp : 58-59° C
IR (Nujol) : 3500, 3400, 1680 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.10-1.55 (12H, m), 1.04-4.45 (8H, m), 5.24 (1H, td, J=20 and 9Hz), 7.65 (1H, t, J=7Hz), 7.32 (1H, t, J=7Hz), 7.90 (1H, d, J=7Hz), 8.17 (1H, d, J=7Hz), 8.29 (2H, q, J=10 and 8Hz), 8.25 (1H, d, J=9Hz)

Preparation 31
Tetraethyl (benzoylaminomethylene)bis(phosphonate)
IR ($CHCl_3$) : 3430, 1665, 1600, 1580, 1480, 1390, 1368 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.31 (6H, t, J=7Hz), 1.35 (6H, t, J=7Hz), 4.05-4.35 (8H, m), 5.26 (1H, dt, J=10, 22Hz), 6.77 (1H, d, J=10Hz), 7.40-7.60 (3H, m), 7.81 (2H, d, J=8Hz)

Preparation 32
Tetraethyl [(4-chlorobenzoylamino)methylene]bis(phosphonate)
NMR ($CDCl_3$, $\delta$) : 1.31 (6H, t, J=7Hz), 1.35 (6H, t, J=7Hz), 4.22 (4H, q, J=7Hz), 4.23 (4H, q, J=7Hz), 5.24 (1H, dt, J=10, 22Hz), 4.23 (4H, q, J=7Hz), 5.24 (1H, dt, J=10, 22Hz), 6.82 (1H, d, J=10Hz), 7.44 (2H, d, J=8Hz), 7.74 (2H, d, J=8Hz)

Preparation 33
Tetraethyl [(2-pyridinecarboxamido)methylene]bis(phosphonate)
IR (Neat) : 3500, 3400, 1685 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.28-1.37 (12H, m), 4.15-4.32 (8H, m), 5.18 (1H, td, J=20 and 10Hz), 7.27-7.51 (1H, m), 7.82-7.91 (1H, td, J=8 and 2Hz), 8.17 (1H, d, J=8Hz), 8.54 (1H, d, J=10Hz), 8.58-8.62 (1H, m)

Preparation 34

To a solution of 2-[1-(tert-butoxycarbonyl)imidazol-4-yl]acetic acid (45 mg) and tetraethyl (aminomethylene)bis(phosphonate) (91 mg) in N,N-dimethylformamide (1 ml) was added N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide hydrochloride (42 mg) with stirring on ice-sodium chloride bath under nitrogen atmosphere. After stirring for 36 hours at 5° C, the mixture was diluted with chloroform (10 ml) and washed with cold 1N aqueous solution of citric acid (10 ml). The aqueous layer was extracted with chloroform (10 ml) twice and the combined organic layers were dried over sodium sulfate and evaporated in vacuo. The residue was dissolved in ethyl acetate (10 ml) and the solution was washed with water (10 ml), dried over sodium sulfate and evaporated in vacuo to give a colorless syrup of tetraethyl [[2-{1-(tert-butoxycarbonyl)-

imidazol-4-yl}acetamido]methylene]bis(phosphonate) (67 mg).
NMR ($CDCl_3$, $\delta$) : 1.32 (6H, t, J = 6Hz), 1.33 (6H, t, J = 6Hz), 1.62 (9H, s), 3.60 (2H, s), 4.1-4.3 (8H, m), 5.06 (1H, dt, J = 12Hz, 24Hz), 7.28 (1H, s), 7.59 (1H, d, J = 12Hz), 8.07 (1H, s)

Preparation 35

To a solution of tetraethyl (aminomethylene)bis(phosphonate) (661 mg) in pyridine (2 ml) were added benzenesulfonyl chloride (0.35 ml) and then 4-(dimethylamino)pyridine (50 mg) at ambient temperature with stirring. After stirring for 4 hours at the same temperature, the reaction mixture was diluted with ethyl acetate (20 ml). The mixture was washed with 1N hydrochloric acid four times, water and saturated aqueous hydrogen bicarbonate solution successively. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (20 g) eluted with a mixture of chloroform and methanol (20:1 V/V) to give tetraethyl (phenylsulfonylaminomethylene)bis(phosphonate) as a yellow syrup (364 mg).
IR ($CHCl_3$) : 3390, 3000, 1343, 1256, 1165 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.25 (6H, t, J = 7Hz), 1.28 (6H, t, J = 7Hz), 3.90-4.20 (8H, m), 4.23 (1H, t, J = 22Hz), 5.68 (1H, br s), 7.45-7.60 (3H, m), 7.91 (2H, dd, J = 2, 8Hz)

The following compounds (Preparations 36 to 40) were obtained according to a similar manner to that of Preparation 35.

Preparation 36
Tetraethyl (tosylaminomethylene)bis(phosphonate)
NMR ($CDCl_3$, $\delta$) : 1.2-1.45 (12H, m), 2.42 (3H, s), 3.9-4.4 (9H, m), 7.3 and 7.75 (4H, ABq, J = 8.4Hz)

Preparation 37
Tetraethyl [(4-chlorophenyl)sulfonylaminomethylene]bis(phosphonate)
mp : 130-131 °C
NMR ($CDCl_3$, $\delta$) : 1.27 (6H, t, J = 6Hz), 1.30 (6H, t, J = 6Hz), 3.90-4.30 (8H, m), 5.32 (1H, br s), 7.48 (2H, d, J = 8Hz), 7.84 (2H, d, J = 8Hz)

Preparation 38
Tetraethyl [(3,4-dichlorophenyl)sulfonylaminomethylene]bis(phosphonate)
mp : 104-106 °C
IR (Nujol) : 3600, 3400, 3000, 1630, 1200, 1160, 1070 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.20-1.40 (12H, m), 4.00-4.40 (9H, m), 7.58 (1H, d, J = 8.5Hz), 7.74 (1H, dd, J = 9.0 and 2Hz), 7.99 (1H, d, J = 2Hz)

Preparation 39
Tetraethyl [(2-thienyl)sulfonylaminomethylene]bis(phosphonate)
IR (Neat) : 3070, 2960, 1255, 1155, 1020 $cm^{-1}$
NMR ($CDCl_3$, $\delta$) : 1.2-1.5 (12H, m), 2.3 (1H, br), 4.0-4.35 (9H, m), 7.09 (1H, dd, J = 4Hz and 5Hz), 7.60 (1H, dd, J = 1Hz and 5Hz), 7.66 (1H, dd, J = 1Hz and 4Hz)

Preparation 40
Tetraethyl [(8-quinolyl)sulfonylaminomethylene]bis(phosphonate)
NMR ($CDCl_3$, $\delta$) : 1.10 (6H, t, J = 7Hz), 1.19 (6H, t, J = 7Hz), 3.80-4.20 (8H, m), 4.40 (1H, t, J = 22Hz), 7.57 (1H, dd, J = 8,4Hz), 7.65 (1H, t, J = 8Hz), 8.06 (1H, d, J = 8Hz), 8.29 (1H, dd, J = 8, 2Hz), 8.33 (1H, d, J = 8Hz), 9.07 (1H, dd, J = 4, 2Hz)

Preparation 41

To a suspension of sodium hydride (44 mg, 63.9% oil dispersion) in distilled tetrahydrofuran (2.0 ml) was added tetraisopropyl methylenebis(phosphonate) (344 mg) in one portion at 5 °C. The mixture was stirred for 30 minutes at ambient temperature and then cooled in an ice bath, followed by addition of 4-chlorophenyl isocyanate (154 mg). The mixture was stirred for 30 minutes at 5 °C and for one hour at ambient temperature to give a solution including sodium salt of tetraisopropyl [N-(4-chlorophenyl)-carbamoylmethylene]bis(phosphonate). Methyl iodide (426 mg) was added thereto at ambient temperature. The solution was stirred for 5 hours at the same temperature and quenched with aqueous solution of

ammonium chloride. The separated oil was extracted with ethyl acetate. The extract was washed with brine, dried, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using a mixture of n-hexane and ethyl acetate (1:1 V/V) as an eluent to give tetraisopropyl 1-[N-(4-chlorophenyl)carbamoyl]ethane-1,1-bis(phosphonate) (399 mg) as a colorless oil.

IR (Nujol) : 3350, 1695 cm-1

NMR ($CDCl_3$, $\delta$) : 1.20-1.55 (24H, m), 1.70 (3H, t, J=14Hz), 4.68-4.92 (4H, m), 7.28 (2H, d, J=8Hz), 7.52 (2H, d, J=8Hz), 9.29 (1H, s)

The following compounds (Examples 1 to 31) were obtained according to a similar manner to that of Preparation 2.

Example 1

Tris(tert-butylamine) salt of [N-(phenyl)thiocarbamoylmethylene]bis(phosphonic acid)

mp : 140°C

NMR ($D_2O$, $\delta$) : 1.35 (27H, br s), 4.05 (1H, t, J=20Hz), 7.3-7.75 (5H, m)

Example 2

Tris(tert-butylamine) salt of [N-(4-chlorophenyl)carbamoylmethylene]bis(phosphonic acid)

mp : 206-210°C

IR (Nujol) : 3700-2000, 1660, 1540, 1150, 1090, 825 $cm^{-1}$

NMR ($D_2O$, $\delta$) : 1.4 (27H, br s), 3.23 (1H, t, J=20Hz), 7.40 and 7.50 (4H, ABq, J=9Hz)

Example 3

Tris(tert-butylamine) salt of [N-(phenyl)carbamoylmethylene]bis(phosphonic acid)

mp : 207-209°C

IR (Nujol) : 3700-2000, 1650, 1600, 1150, 1130, 1065, 960 $cm^{-1}$

NMR ($D_2O$, $\delta$) : 1.40 (27H, br s), 3.25 (1H, t, J=20Hz), 7.15-7.6 (5H, m)

Example 4

Tris(tert-butylamine) salt of [N-(4-fluorophenyl)carbamoylmethylene]bis(phosphonic acid)

mp : 209-211°C

IR (Nujol) : 3700-2000 (br), 1650 $cm^{-1}$

NMR ($D_2O$, $\delta$) : 1.36 (27H, s), 3.23 (1H, t, J=20Hz), 7.14 (2H, t, J=8Hz), 7.50 (2H, dd, J=8 and 5Hz)

Example 5

Tris(tert-butylamine) salt of [N-(3,4-dichlorophenyl)carbamoylmethylene]bis(phosphonic acid)

mp : 216-220°C

IR (Nujol) : 3600-2100 (br), 1660 $cm^{-1}$

NMR ($D_2O$, $\delta$) : 1.35 (27H, s), 3.30 (1H, t, J=20Hz), 7.38 (1H, dd, J=9 and 2Hz), 7.50 (1H, d, J=9Hz), 7.81 (1H, d, J=2Hz)

Example 6

Tris(tert-butylamine) salt of [N-(p-tolyl)carbamoylmethylene]bis(phosphonic acid)

mp : 221-230°C

IR (Nujol) : 3700-2000 (br), 1655 $cm^{-1}$

NMR ($D_2O$, $\delta$) : 1.36 (27H, s), 2.32 (3H, s), 3.27 (1H, t, J=20Hz), 7.25 (2H, d, J=8Hz), 7.40 (2H, d, J=8Hz)

Example 7

Tris(tert-butylamine) salt of [N-(4-methoxyphenyl)carbamoylmethylene]bis(phosphonic acid)

mp : 214-220°C

IR (Nujol) : 3700-2300 (br), 1650 $cm^{-1}$

NMR ($D_2O$, $\delta$) : 1.37 (27H, s), 3.27 (1H, t, J=20Hz), 3.85 (3H, s), 7.02 (2H, d, J=8Hz), 7.45 (2H, d, J=8Hz)

Example 8

Tris(tert-butylamine) salt of 1-[N-(4-chlorophenyl)carbamoyl]ethane-1,1-bis(phosphonic acid)

mp : 237-239°C

IR (Nujol) : 3700-2000 (br), 1650 $cm^{-1}$

NMR ($D_2O$, $\delta$) : 1.36 (27H, s), 1.56 (3H, t, J=14Hz), 7.38 (2H, d, J=8Hz), 7.50 (2H, d, J=8Hz)

Example 9
Tris(tert-butylamine) salt of [N-(4-chlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 206-208 °C
NMR ($D_2O$, δ) : 1.34 (27H, m), 4.08 (1H, t, J = 22Hz), 7.47 and 7.60 (4H, ABq, J = 8Hz)

Example 10
Bis(tert-butylamine) salt of [N-(1-naphthyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 160 °C (dec.)
NMR ($D_2O$, δ) : 1.35 (18H, s), 4.24 (1H, t, J = 22Hz), 7.60-8.23 (7H, m)

Example 11
Disodium salt of [N-(3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 218 °C (dec.)
IR (Nujol) : 3300, 1600, 1410, 1170, 1130, 1070, 890 $cm^{-1}$
NMR ($D_2O$, δ) : 4.21 (1H, t, J = 20Hz), 7.60-7.77 (2H, m), 7.82 (1H, m), 8.10 (1H, s)

Example 12
Disodium salt of [N-(4-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 218 °C (dec.)
IR (Nujol) : 3260, 1610, 1425, 1400, 1335, 1170, 1065 $cm^{-1}$
NMR ($D_2O$, δ) : 4.11 (1H, t, J = 20.7Hz), 7.80 and 7.88 (4H, ABq, J = 8.8Hz)

Example 13
Disodium salt of [N-(3-chlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 224 °C (dec.)
IR (Nujol) : 3300, 3200, 2350, 1595, 1400, 1255, 1200, 1170, 1090 $cm^{-1}$
NMR ($D_2O$, δ) : 4.12 (1H, t, J = 20Hz), 7.31-7.56 (3H, m), 7.88 (1H, s)

Example 14
Disodium salt of [N-(2-chlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 255-257 °C (dec.)
IR (Nujol) : 3700-2400 (br), 1590, 1150, 1120 $cm^{-1}$

Example 15
Disodium salt of [N-(4-fluorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 247-249 °C (dec.)
IR (Nujol) : 3700-2300 (br), 1220, 1090 $cm^{-1}$
NMR ($D_2O$, δ) : 4.10 (1H, t, J = 21Hz), 7.21 (2H, t, J = 9Hz), 7.58 (2H, dd, J = 9 and 5Hz)

Example 16
Disodium salt of [N-(p-tolyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 255-258 °C (dec.)
IR (Nujol) : 3700-2300 (br.), 1520, 1150 $cm^{-1}$
NMR ($D_2O$, δ) : 2.37 (3H, s), 4.04 (1H, t, J = 20Hz), 7.32 and 7.52 (2H, dd, J = 8Hz)

Example 17
Disodium salt of [N-(2-methoxyphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 227 °C (dec.)
IR (Nujol) : 3605, 3350, 1600, 1540, 1400, 1240, 1160, 1050 $cm^{-1}$
NMR ($D_2O$, δ) : 3.90 (3H, s), 4.09 (1H, t, J = 20Hz), 7.03-7.19 (2H, m), 7.37 (1H, t, J = 8Hz), 8.14 (1H, d, J = 8Hz)

Example 18
Disodium salt of [N-(3,4-dichlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 248-250 °C (dec.)
IR (Nujol) : 3700-2300 (br), 1190, 1090 $cm^{-1}$
NMR ($D_2O$, δ) : 4.03 (1H, t, J = 20Hz), 7.53-7.64 (2H, m), 8.03 (1H, s)

Example 19

Disodium salt of [N-(2-pyridyl)carbamoylmethylene]bis(phosphonic acid)
mp : >300 °C
IR (Nujol) : 3700-2100 (br), 1675 $cm^{-1}$
NMR ($D_2O$, δ) : 3.47 (1H, t, J = 20Hz), 7.27 (1H, t, J = 6Hz), 7.83 (1H, d, J = 8Hz), 7.95 (1H, t, J = 8Hz), 8.29 (1H, d, J = 6Hz)

Example 20
Disodium salt of [N-(2-benzo[b]thienyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : >280 °C
IR (Nujol) : 3700-2300 (br), 1460, 1410, 1230, 1160 $cm^{-1}$
NMR ($D_2O$, δ) : 4.02 (1H, t, J = 20Hz), 7.35-7.47 (2H, m), 7.45 (1H, s), 7.85 (1H, d, J = 11Hz), 7.97 (1H, d, J = 15Hz)

Example 21
Disodium salt of [N-(2-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 212 °C (dec.)
IR (Nujol) : 3250, 2400, 1530, 1410, 1320, 1150, 1060 $cm^{-1}$
NMR ($D_2O$, δ) : 4.16 (1H, t, J = 21Hz), 7.52-7.60 (1H, m), 7.65-7.76 (2H, m), 7.83 (1H, d, J = 8Hz)

Example 22
Disodium salt of [N-(4-chloro-3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 245 °C (dec.)
IR (Nujol) : 3350, 3200, 1620, 1560, 1485, 1415, 1320 $cm^{-1}$
NMR ($D_2O$, δ) : 4.00 (1H, t, J = 20Hz), 7.68 (1H, d, J = 9Hz), 7.88 (1H, d, J = 9Hz), 8.29 (1H, s)

Example 23
Disodium salt of [N-(4-methoxy-3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 249-252 °C (dec.)
IR (Nujol) : 3250, 2350, 1505, 1325, 1280, 1130 $cm^{-1}$
NMR ($D_2O$, δ) : 4.05 (1H, t, J = 20Hz), 7.28 (1H, d, J = 9Hz), 7.77 (1H, d, J = 9Hz), 7.97 (1H, d, J = 2Hz)

Example 24
Bis(tert-butylamine) salt of (N-methylcarbamoylmethylene)bis(phosphonic acid)
mp : 229 °C (dec.)
IR (Nujol) : 3600-2000, 1645, 1150 $cm^{-1}$
NMR ($D_2O$, δ) : 1.36 (18H, s), 2.79 (3H, s), 3.22 (1H, t, J = 21Hz)

Example 25
Disodium salt of[N-(n-butyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : >250 °C
IR (Nujol) : 3500, 3250, 1560, 1280, 1180, 1065 $cm^{-1}$
NMR ($D_2O$, δ) : 0.94 (3H, t, J = 7Hz), 1.33-1.51 (2H, m), 1.51-1.69 (2H, m), 3.61 (2H, t, J = 8Hz), 3.91 (1H, t, J = 21Hz)

Example 26
Disodium salt of [N-(4-trifluoromethylphenyl)carbamoylmethylene]bis(phosphonic acid)
mp : >250 °C
IR (Nujol) : 3700-3000 (br), 2300, 1650, 1600, 1335, 1100 $cm^{-1}$
NMR ($D_2O$, δ) : 3.31 (1H, t, J = 20Hz), 7.70 (4H, s)

Example 27
Disodium salt of [N-(4-methylthiophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 215 °C (dec.)
IR (Nujol) : 3500, 3300, 1500, 1390, 1170, 1065 $cm^{-1}$
NMR ($D_2O$, δ) : 2.5 (1H, s), 4.09 (1H, t, J = 21Hz), 7.4 (2H, d, J = 8.6Hz), 7.59 (2H, d, J = 8.6Hz)

Example 28
Disodium salt of [N-(4-mesylaminophenyl)thiocarbamoylmethylene]bis(phosphonic acid)

mp : 225° C (dec.)
IR (Nujol) : 3200, 2350, 1510, 1320, 1150 $cm^{-1}$
NMR ($D_2O$, δ) : 3.12 (3H, s), 4.08 (1H, t, J = 20Hz), 7.34 and 7.65 (each 2H, d, J = 9Hz)

Example 29
Disodium salt of [N-(3-mesylaminophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 212° C (dec.)
IR (Nujol) : 3300, 2400, 1620, 1340, 1160, 1080 $cm^{-1}$
NMR ($D_2O$, δ) : 3.12 (3H, s), 4.80 (1H, t, J = 20Hz), 7.22-7.25 (1H, br d, J = 6Hz), 7.45-7.49 (2H, m), 7.73 (1H, br s)

Example 30
Disodium salt of [N-(4-acetylaminophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 218° C (dec.)
IR (Nujol) : 3250, 2350, 1660, 1510, 1400, 1140, 1060 $cm^{-2}$
NMR ($D_2O$, δ) : 2.18 (3H, s), 4.80 (1H, t, J = 20Hz), 7.50 and 7.64 (2H, d, J = 8Hz)

Example 31
Disodium salt of [N-(3-acetylaminophenyl)thiocarbamoyl]methylenebis(phosphonic acid)
mp : 209° C (dec.)
IR (Nujol) : 3200, 2350, 1670, 1605, 1550, 1160, 1080 $cm^{-1}$
NMR ($D_2O$, δ) : 2.16 (3H, s), 4.80 (1H, t, J = 20Hz), 7.35-7.57 (2H, m), 7.76 (1H, br s)

The following compounds (Examples 32 to 37) were obtained according to a similar manner to that of Preparation 29.

Example 32
Bis(tert-butylamine)salt of [(2-benzo[b]thiophenecarboxamido)methylene]bis(phosphonic acid)
mp : 234-238° C
IR (Nujol) : 3700-2050 (br), 1640 $cm^{-1}$
NMR ($D_2O$, δ) : 1.40 (18H, s), 4.59 (1H, t, J = 20Hz), 7.43-7.58 (2H, m), 7.95-8.08 (2H, m), 8.11 (1H, s)

Example 33
Tris(tert-butylamine)salt of [(2-quinolinecarboxamido)methylene]bis(phosphonic acid)
IR (Nujol) : 3700-2000 (br), 1660 $cm^{-1}$
NMR ($D_2O$, δ) : 1.46 (27H, s), 4.61 (1H, t, J = 20Hz), 7.76 (1H, t, J = 11Hz), 7.94 (1H, t, J = 11Hz), 8.08 (1H, d, J = 8Hz), 8.20 (2H, t, J = 11Hz), 8.58 (1H, d, J = 8Hz)

Example 34
Disodium salt of (benzoylaminomethylene)bis(phosphonic acid)
mp : >260° C
NMR ($D_2O$, δ) : 4.66 (1H, t, J = 20Hz), 7.20-7.50 (3H, m), 7.85 (2H, d, J = 8Hz)

Example 35
Disodium salt of [(4-chlorobenzoylamino)methylene]bis(phosphonic acid)
mp : >260° C
NMR ($D_2O$, δ) : 4.65 (1H, t, J = 20Hz), 7.55 (2H, d, J = 9Hz), 7.83 (2H, d, J = 9Hz)

Example 36
Disodium salt of [(2-pyridinecarboxamido)methylene]bis(phosphonic acid)
mp : >300° C
IR (Nujol) : 3700-2300 (br), 1670 $cm^{-1}$
NMR ($D_2O$, δ) : 4.64 (1H, t, J = 20Hz), 7.64-7.71 (1H, m), 8.04-8.14 (2H, m), 8.66 (1H, d, J = 5Hz)

Example 37
[{2-(Imidazol-4-yl)acetamido}methylene]bis(phosphonic acid)
mp : 247-250° C
NMR ($D_2O$, δ) : 3.77 (2H, s), 4.55 (1H, t, J = 21Hz), 7.24 (1H, s), 8.51 (1H, s)

The following compounds (Examples 38 to 43) were obtained according to a similar manner to that of Preparation 35.

Example 38
(Phenylsulfonylaminomethylene)bis(phosphonic acid)
mp : 215-216 °C
NMR ($D_2O$, δ) : 3.95 (1H, t, J = 21Hz), 7.50-7.70 (3H, m), 7.89 (1H, dd, J = 1, 8Hz)

Example 39
(Tosylaminomethylene)bis(phosphonic acid)
mp : 232-233 °C
NMR ($D_2O$, δ) : 3.98 (1H, t, J = 21Hz), 7.78 and 7.41 (4H, ABq, J = 8.1Hz)

Example 40
Disodium salt of [(4-chlorophenyl)sulfonylaminomethylene]bis(phosphonic acid)
mp : >260 °C
NMR ($D_2O$, δ) : 3.80 (1H, t, J = 20Hz), 7.59 (2H, d, J = 8Hz), 7.88 (2H, d, J = 8Hz)

Example 41
[(3,4-Dichlorophenyl)sulfonylaminomethylene]bis(phosphonic acid)
mp : >250 °C
IR (Nujol) : 3100, 1345, 1270, 1230, 1050 $cm^{-1}$
NMR ($D_2O$, δ) : 3.74 (1H, t, J = 20Hz), 7.70 (1H, d, J = 9Hz), 7.80 (1H, d, J = 9Hz), 8.09 (1H, s)

Example 42
[(2-Thienyl)sulfonylaminomethylene]bis(phosphonic acid)
mp : 231 °C (dec.)
IR (Nujol) : 3540, 1325, 1165 $cm^{-1}$
NMR ($D_2O$, δ): 3.98 (1H, t, J = 21Hz), 7.1-7.2 (1H, m), 7.73 (1H, d, J = 3.5Hz), 7.79 (1H, d, J = 5Hz)

Example 43
Disodium salt of [(8-quinolyl)sulfonylaminomethylene]bis(phosphonic acid)
mp : >260 °C
NMR ($D_2O$, δ) : 3.65 (1H, t, J = 19Hz), 7.61 (1H, dd, J = 3, 7Hz), 7.65 (1H, t, J = 7Hz), 8.11 (1H, d, J = 7Hz), 8.40 (1H, d, J = 7Hz), 8.44 (1H, d, J = 7Hz), 8.96 (1H, d, J = 3Hz)

Example 44

To a solution of tetraisopropyl [N-(phenyl)thiocarbamoylmethylene]bis(phosphonate) (0.101 g) in methylene chloride (4 ml) was added iodotrimethylsilane (0.18 ml) in one portion at 5 °C. The mixture was stirred for 30 minutes at ambient temperature and then extracted with water. The aqueous layer was washed with methylene chloride and the solvent was removed azeotropically with toluene under reduced pressure. The residue containing [N-(phenyl)thiocarbamoylmethylene]bis(phosphonic acid) was dissolved in ethanol (2.1 ml) and tert-butylamine (0.11 ml) was added thereto. The solvent was removed and the residue was pulverized with a mixture of ethanol and diethyl ether. The powder was dissolved in water and lyophilized to give tris(tert-butylamine)salt of [N-(phenyl)thiocarbamoylmethylene]bis(phosphonic acid) (93 mg) as a colorless powder.
mp : 140 °C
NMR ($D_2O$, δ) : 1.35 (27H, br s), 4.05 (1H, t, J = 20Hz), 7.3-7.75 (5H, m)

The following compounds (Examples 45 to 54) were obtained according to a similar manner to that of Example 44.

Example 45
Tris(tert-butylamine) salt of [N-(4-chlorophenyl)carbamoylmethylene]bis(phosphonic acid)
mp : 206-210 °C
IR (Nujol) : 3700-2000, 1660, 1540, 1150, 1090, 825 $cm^{-1}$
NMR ($D_2O$, δ) : 1.4 (27H, br s), 3.23 (1H, t, J = 20Hz), 7.40 and 7.50 (4H, ABq, J = 9Hz)

Example 46
Tris(tert-butylamine) salt of [N-(phenyl)carbamoylmethylene]bis(phosphonic acid)
mp : 207-209 °C
IR (Nujol) : 3700-2000, 1650, 1600, 1150, 1130, 1065, 960 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.40 (27H, br s), 3.25 (1H, t, J = 20Hz), 7.15-7.6 (5H, m)

Example 47 Tris(tert-butylamine) salt of [N-(4-fluorophenyl)carbamoylmethylene]bis(phosphonic acid)
mp : 209-211 °C
IR (Nujol) : 3700-2000 (br), 1650 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.36 (27H, s), 3.23 (1H, t, J = 20Hz), 7.14 (2H, t, J = 8Hz), 7.50 (2H, dd, J = 8 and 5Hz)

Example 48
Tris(tert-butylamine) salt of [N-(3,4-dichlorophenyl)carbamoylmethylene]bis(phosphonic acid)
mp : 216-220 °C
IR (Nujol) : 3600-2100 (br), 1660 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.35 (27H, s), 3.30 (1H, t, J = 20Hz), 7.38 (1H, dd, J = 9 and 2Hz), 7.50 (1H, d, J = 9Hz), 7.81 (1H, d, J = 2Hz)

Example 49
Tris(tert-butylamine) salt of [N-(p-tolyl)carbamoylmethylene]bis(phosphonic acid)
mp : 221-230 °C
IR (Nujol) : 3700-2000 (br), 1655 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.36 (27H, s), 2.32 (3H, s), 3.27 (1H, t, J = 20Hz), 7.25 (2H, d, J = 8Hz), 7.40 (2H, d, J = 8Hz)

Example 50
Tris(tert-butylamine) salt of [N-(4-methoxyphenyl)carbamoylmethylene]bis(phosphonic acid)
mp : 214-220 °C
IR (Nujol) : 3700-2300 (br), 1650 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.37 (27H, s), 3.27 (1H, t, J = 20Hz), 3.85 (3H, s), 7.02 (2H, d, J = 8Hz), 7.45 (2H, d, J = 8Hz)

Example 51
Tris(tert-butylamine) salt of 1-[N-(4-chlorophenyl)carbamoyl]ethane-1,1-bis(phosphonic acid)
mp : 237-239 °C
IR (Nujol) : 3700-2000 (br), 1650 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.36 (27H, s), 1.56 (3H, t, J = 14Hz), 7.38 (2H, d, J = 8Hz), 7.50 (2H, d, J = 8Hz)

Example 52
Tris(tert-butylamine) salt of [N-(4-chlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 206-208 °C
NMR ($D_2O$, $\delta$) : 1.34 (27H, m), 4.08 (1H, t, J = 22Hz), 7.47 and 7.60 (4H, ABq, J = 8Hz)

Example 53
Bis(tert-butylamine) salt of [N-(1-naphthyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 160 °C (dec.)
NMR ($D_2O$, $\delta$) : 1.35 (18H, s), 4.24 (1H, t, J = 22Hz), 7.60-8.23 (7H, m)

Example 54
Bis(tert-butylamine) salt of (N-methylcarbamoylmethylene)bis(phosphonic acid)
mp : 229 °C (dec.)
IR (Nujol) : 3600-2000, 1645, 1150 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.36 (18H, s), 2.79 (3H, s), 3.22 (1H, t, J = 21Hz)

Example 55

To a solution of tetraisopropyl [N-(3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonate) (2 g) in methylene chloride (36 ml) was added iodotrimethylsilane (2.86 ml) at 0 °C and the mixture was stirred for 4 hours at the same temperature. Water (40 ml) was poured into the reaction mixture and the separated aqueous layer was washed four times with methylene chloride and concentrated. The residue was dissolved

in acetonitrile (30 ml) and tert-butylamine (534 mg) was added thereto. The resulting precipitate was collected by filtration and tert-butylamine (534 mg) was added to the filtrate. The resulting precipitate was collected by filtration. The obtained precipitates were combined and passed through the column chromatography on Dowex 50W × 8 ($H^+$, 5 ml) (Trademark : manufactured by Dow Chemical Co.) with water. The eluents were concentrated and the residue containing [N-(3-trifluoromethylphenyl)thiocarbamoylmethylene]-bis(phosphonic acid) was dissolved in water (20 ml). To the solution was added sodium acetate (266 mg) and the mixture was stirred at 60°C for 20 minutes and then heated at 100°C with adding ethanol thereto. After the mixture was cooled, the resulting precipitate was collected by filtration and dried in vacuo to give disodium salt of [N-(3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid) (544 mg).

mp : 218°C (dec.)
IR (Nujol) : 3300, 1600, 1410, 1170, 1130, 1070, 890 $cm^{-1}$
NMR ($D_2O$, δ) : 4.21 (1H, t, J = 20Hz), 7.60-7.77 (2H, m), 7.82 (1H, m), 8.10 (1H, s)

The following compounds (Examples 56 to 74) were obtained according to a similar manner to that of Example 55.

Example 56
Disodium salt of [N-(4-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 218°C (dec.)
IR (Nujol) : 3260, 1610, 1425, 1400, 1335, 1170, 1065 $cm^{-1}$
NMR ($D_2O$, δ) : 4.11 (1H, t, J = 20.7Hz), 7.80 and 7.88 (4H, ABq, J = 8.8Hz)

Example 57
Disodium salt of [N-(3-chlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 224°C (dec.)
IR (Nujol) : 3300, 3200, 2350, 1595, 1400, 1255, 1200, 1170, 1090 $cm^{-1}$
NMR ($D_2O$, δ) : 4.12 (1H, t, J = 20Hz), 7.31-7.56 (3H, m), 7.88 (1H, s)

Example 58
Disodium salt of [N-(2-chlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 255-257°C (dec.)
IR (Nujol) : 3700-2400 (br), 1590, 1150, 1120 $cm^{-1}$

Example 59
Disodium salt of [N-(4-fluorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 247-249°C (dec.)
IR (Nujol) : 3700-2300 (br), 1220, 1090 $cm^{-1}$
NMR ($D_2O$, δ) : 4.10 (1H, t, J = 21Hz), 7.21 (2H, t, J = 9Hz), 7.58 (2H, dd, J = 9 and 5Hz)

Example 60
Disodium salt of [N-(p-tolyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 255-258°C (dec.)
IR (Nujol) : 3700-2300 (br), 1520, 1150 $cm^{-1}$
NMR ($D_2O$, δ) : 2.37 (3H, s), 4.04 (1H, t, J = 20Hz), 7.32 and 7.52 (2H, dd, J = 8Hz)

Example 61
Disodium salt of [N-(2-methoxyphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 227°C (dec.)
IR (Nujol) : 3605, 3350, 1600, 1540, 1400, 1240, 1160, 1050 $cm^{-1}$
NMR ($D_2O$, δ) : 3.90 (3H, s), 4.09 (1H, t, J = 20Hz), 7.03-7.19 (2H, m), 7.37 (1H, t, J = 8Hz), 8.14 (1H, d, J = 8Hz)

Example 62
Disodium salt of [N-(3,4-dichlorophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 248-250°C (dec.)
IR (Nujol) : 3700-2300 (br), 1190, 1090 $cm^{-1}$
NMR ($D_2O$, δ) : 4.03 (1H, t, J = 20Hz), 7.53-7.64 (2H, m), 8.03 (1H, s)

Example 63
Disodium salt of [N-(2-pyridyl)carbamoylmethylene]bis(phosphonic acid)

mp : >300° C
IR (Nujol) : 3700-2100 (br), 1675 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 3.47 (1H, t, J = 20Hz), 7.27 (1H, t, J = 6Hz), 7.83 (1H, d, J = 8Hz), 7.95 (1H, t, J = 8Hz), 8.29 (1H, d, J = 6Hz)

Example 64
Disodium salt of [N-(2-benzo[b]thienyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : >280° C
IR (Nujol) : 3700-2300 (br), 1460, 1410, 1230, 1160 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 4.02 (1H, t, J = 20Hz), 7.35-7.47 (2H, m), 7.45 (1H, s), 7.85 (1H, d, J = 11Hz), 7.97 (1H, d, J = 15Hz)

Example 65
Disodium salt of [N-(2-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 212° C (dec.)
IR (Nujol) : 3250, 2400, 1530, 1410, 1320, 1150, 1060 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 4.16 (1H, t, J = 21Hz), 7.52-7.60 (1H, m), 7.65-7.76 (2H, m), 7.83 (1H, d, J = 8Hz)

Example 66
Disodium salt of [N-(4-chloro-3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 245° C (dec.)
IR (Nujol) : 3350, 3200, 1620, 1560, 1485, 1415, 1320 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 4.00 (1H, t, J = 20Hz), 7.68 (1H, d, J = 9Hz), 7.88 (1H, d, J = 9Hz), 8.29 (1H, s)

Example 67
Disodium salt of [N-(4-methoxy-3-trifluoromethylphenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 249-252° C (dec.)
IR (Nujol) : 3250, 2350, 1505, 1325, 1280, 1130 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 4.05 (1H, t, J = 20Hz), 7.28 (1H, d, J = 9Hz), 7.77 (1H, d, J = 9Hz), 7.97 (1H, d, J = 2Hz)

Example 68
Disodium salt of [N-(n-butyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : >250° C
IR (Nujol) : 3500, 3250, 1560, 1280, 1180, 1065 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 0.94 (3H, t, J = 7Hz), 1.33-1.51 (2H, m), 1.51-1.69 (2H, m), 3.61 (2H, t, J = 8Hz), 3.91 (1H, t, J = 21Hz)

Example 69
Disodium salt of [N-(4-trifluoromethylphenyl)carbamoylmethylene]bis(phosphonic acid)
mp : >250° C
IR (Nujol) : 3700-3000 (br), 2300, 1650, 1600, 1335, 1100 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 3.31 (1H, t, J = 20Hz), 7.70 (4H, s)

Example 70
Disodium salt of [N-(4-methylthiophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 215° C (dec.)
IR (Nujol) : 3500, 3300, 1500, 1390, 1170, 1065 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 2.5 (1H, s), 4.09 (1H, t, J = 21Hz), 7.4 (2H, d, J = 8.6Hz), 7.59 (2H, d, J = 8.6Hz)

Example 71
Disodium salt of [N-(4-mesylaminophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 225° C (dec.)
IR (Nujol) : 3200, 2350, 1510, 1320, 1150 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 3.12 (3H, s), 4.08 (1H, t, J = 20Hz), 7.34 and 7.65 (each 2H, d, J = 9Hz)

Example 72
Disodium salt of [N-(3- mesylaminophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 212° C (dec.)

IR (Nujol) : 3300, 2400, 1620, 1340, 1160, 1080 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 3.12 (3H, s), 4.80 (1H, t, J = 20Hz), 7.22-7.25 (1H, br d, J = 6Hz), 7.45-7.49 (2H, m), 7.73 (1H, br s)

Example 73
Disodium salt of [N-(4-acetylaminophenyl)thiocarbamoylmethylene]bis(phosphonic acid)
mp : 218° C (dec.)
IR (Nujol) : 3250, 2350, 1660, 1510, 1400, 1140, 1060 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 2.18 (3H, s), 4.80 (1H, t, J = 20Hz), 7.50 and 7.64 (2H, d, J = 8Hz)

Example 74
Disodium salt of [N-(3-acetylaminophenyl)thiocarbamoyl]methylenebis(phosphonic acid)
mp : 209° C (dec.)
IR (Nujol) : 3200, 2350, 1670, 1605, 1550, 1160, 1080 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 2.16 (3H, s), 4.80 (1H, t, J = 20Hz), 7.35-7.57 (2H, m), 7.76 (1H, br s)

Example 75

Tris(tert-butylamine) salt of [N-(phenyl)thiocarbamoylmethylene]bis(phosphonic acid) (9.07 g) was passed through the column chromatography on Dowex 50W × 8 ($H^+$, 76 ml) with water and the eluents were concentrated to give the residue containing [N-(phenyl)thiocarbamoylmethylene]bis(phosphonic acid). To 1M aqueous solution of sodium acetate (34.2 ml) was added the solution of the obtained residue in water (34.2 ml) and the mixture was stirred for 30 minutes. After ethanol (160 ml) was added thereto, the mixture was heated to give a precipitate. The mixture was cooled and the resulting precipitate was collected by filtration to give disodium salt of [N-(phenyl)thiocarbamoylmethylene]bis(phosphonic acid) (6.07 g).
mp : 216° C (dec.)
IR (Nujol) : 3500, 3300, 1505, 1175, 1145, 920 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 4.10 (1H, t, J = 21Hz), 7.3-7.75 (5H, m)

Example 76

To a solution of tetraethyl [(2-benzo[b]thiophenecarboxamido)methylene]bis(phosphonate) (463 mg) in methylene chloride (2 ml) was added iodotrimethylsilane (1 ml) in one portion at 5° C. The mixture was stirred for one hour at 5° C, allowed to stand for 2 days in a refrigerator and then additionally stirred for one hour at ambient temperature. The mixture was extracted with water. The aqueous layer was washed with methylene chloride and diethyl ether and then evaporated under reduced pressure. The residue was dissolved in water and therein tert-butylamine (183 mg) was added. The mixture was lyophilized to give bis-(tert-butylamine)salt of [(2-benzo[b]thiophenecarboxamido)methylene]bis(phosphonic acid) (277 mg) as a white powder.
mp : 234-238° C
IR (Nujol) : 3700-2050 (br), 1640 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.40 (18H, s), 4.59 (1H, t, J = 20Hz), 7.43-7.58 (2H, m), 7.95-8.08 (2H, m), 8.11 (1H, s)

Example 77

Tris(tert-butylamine)salt of [(2-quinolinecarboxamido)methylene]bis(phosphonic acid) was obtained according to a similar manner to that of Example 76.
IR (Nujol) : 3700-2000 (br), 1660 $cm^{-1}$
NMR ($D_2O$, $\delta$) : 1.46 (27H, s), 4.61 (1H, t, J = 20Hz), 7.76 (1H, t, J = 11Hz), 7.94 (1H, t, J = 11Hz), 8.08 (1H, d, J = 8Hz), 8.20 (2H, t, J = 11Hz), 8.58 (1H, d, J = 8Hz)

Example 78

[(2-Pyridinecarboxamido)methylene]bis(phosphonic acid) was obtained according to a similar manner to that of Example 76.
mp : 277° C (dec.)
IR (Nujol) : 3150, 1670, 1640, 1615 cm-1
NMR (DMSO-$d_6$, $\delta$) : 4.60 (1H, td, J = 20 and 10Hz), 7.63-7.70 (1H, m), 8.00-8.10 (1H, m), 8.37 (1H, d, J = 10Hz),

8.70 (lH, br d, J = 5Hz)

A mixture of [(2-pyridinecarboxamido)methylene]bis(phosphonic acid) (l80 mg) and sodium acetate trihydrate (l65 mg) in water (2 ml) was stirred for 30 minutes at ambient temperature, and then filtered. Ethanol (6 ml) was added to the filtrate to give a suspension. This suspension was heated and insoluble material was filtered off. The filtrate was allowed to stand and the precipitate was collected to give disodium salt of [(2-pyridinecarboxamido)methylene]bis(phosphonic acid)(l3l mg) as a white powder.

mp : >300 °C

IR (Nujol) : 3700-2300 (br), l670 $cm^{-1}$

NMR ($D_2O$, $\delta$) : 4.64 (lH, t, J = 20Hz), 7.64-7.7l (lH, m), 8.04-8.l4 (2H, m), 8.66 (lH, d, J = 5Hz)

The following compounds (Examples 79 and 80) were obtained according to a similar manner to that of Example 78.

Example 79

Disodium salt of (benzoylaminomethylene)bis(phosphonic acid)

mp : >260 °C

NMR ($D_2O$, $\delta$) : 4.66 (lH, t, J = 20Hz), 7.20-7.50 (3H, m), 7.85 (2H, d, J = 8Hz)

Example 80

Disodium salt of [(4-chlorobenzoylamino)methylene]bis(phosphonic acid)

mp : >260 °C

NMR ($D_2O$, $\delta$) : 4.65 (lH, t, J = 20Hz), 7.55 (2H, d, J = 9Hz), 7.83 (2H, d, J = 9Hz)

Example 8l

To a solution of tetraethyl [[2-{l-(tertbutoxycarbonyl)imidazol-4-yl}acetamido]methylene]bis-(phosphonate) (67 mg) in methylene chloride (l ml) was added iodotrimethylsilane (0.l2 ml) dropwise with stirring on an ice-water bath under nitrogen atmosphere. The mixture was stirred for l hour under the same condition and then for 2 hours at ambient temperature. After added water (l ml) with stirring under ice-cooling, the mixture was stirred for l5 minutes. To the mixture were added water (4 ml) and chloroform (4 ml). The separated aqueous layer was washed with chloroform (5 ml) four times and concentrated under reduced pressure to give a yellow syrup (70 mg).

The syrup was dissolved in water (0.5 ml) and stirred for 3 hours at ambient temperature to give a white precipitate. The precipitate was filtered and washed with cold water (l ml) to give a white powder of [{2-(imidazol-4-yl)acetamido}methylene]bis(phosphonic acid) (20 mg).

mp : 247-250 °C

NMR ($D_2O$, $\delta$) : 3.77 (2H, s), 4.55 (lH, t, J = 2lHz), 7.24 (lH, s), 8.5l (lH, s)

Example 82

To a solution of tetraethyl (phenylsulfonylaminomethylene)bis(phosphonate) (400 mg) in methylene chloride (4 ml), was added iodotrimethylsilane (0.8 ml) dropwise with stirring under nitrogen gas atmosphere in an ice-water bath. The mixture was stirred for 30 minutes at the same condition and then at ambient temperature for l.5 hours. To the reaction mixture were added water (l0 ml) and chloroform (8 ml) under ice-water bath cooling. The separated aqueous layer was washed with chloroform until its color disappeared and then evaporated in reduced pressure. The residue was washed with ethanol to give white powder of (phenylsulfonylaminomethylene)bis(phosphonic acid) (l94 mg).

mp : 2l5-2l6 °C

NMR ($D_2O$, $\delta$) : 3.95 (lH, t, J = 2lHz), 7.50-7.70 (3H, m), 7.89 (lH, dd, J = l, 8Hz)

The following compounds (Examples 83 to 86) were obtained according to a similar manner to that of Example 82.

Example 83

(Tosylaminomethylene)bis(phosphonic acid)

mp : 232-233 °C

NMR ($D_2O$, $\delta$) : 3.98 (lH, t, J = 2lHz), 7.78 and 7.4l (4H, ABq, J = 8.lHz)

Example 84

[(4-Chlorophenyl)sulfonylaminomethylene]bis(phosphonic acid)

mp : 255-256° C (dec.)
NMR ($D_2O$, δ) : 3.94 (lH, t, J=22Hz), 7.60 (2H, d, J=8Hz), 7.88 (2H, d, J=8Hz)

Disodium salt of [(4-chlorophenyl)sulfonylaminomethylene]bis(phosphonic acid) was obtained according to a similar manner to that of Example 78 from [(4-chlorophenyl)sulfonylaminomethylene]bis(phosphonic acid) and sodium acetate trihydrate.
mp : >260° C
NMR ($D_2O$, δ) : 3.80 (lH, t, J=20Hz), 7.59 (2H, d, J=8Hz), 7.88 (2H, d, J=8Hz)

Example 85
[(3,4-Dichlorophenyl)sulfonylaminomethylene]bis(phosphonic acid)
mp : >250° C
IR (Nujol) : 3l00, l345, l270, l230, l050 $cm^{-1}$
NMR ($D_2O$, δ) : 3.74 (lH, t, J=20Hz), 7.70 (lH, d, J=9Hz), 7.80 (lH, d, J=9Hz), 8.09 (lH, s)

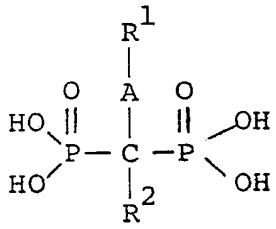
Example 86
[(2-Thienyl)sulfonylaminomethylene]bis(phosphonic acid)
mp : 23l° C (dec.)
IR (Nujol) : 3540, l325, ll65 $cm^{-1}$
NMR ($D_2O$, δ) : 3.98 (lH, t, J=2lHz), 7.l-7.2 (lH, m), 7.73 (lH, d, J=3.5Hz), 7.79 (lH, d, J=5Hz)

Example 87

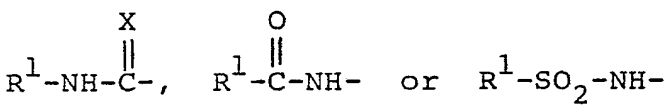
Disodium salt of [(8-quinolyl)sulfonylaminomethylene]bis(phosphonic acid) was obtained according to a similar manner to that of Example 84.
mp : >260° C
NMR ($D_2O$, δ) : 3.65 (lH, t, J=l9Hz), 7.6l (lH, dd, J=3, 7Hz), 7.65 (lH, t, J=7Hz), 8.ll (lH, d, J=7Hz), 8.40 (lH, d, J=7Hz), 8.44 (lH, d, J=7Hz), 8.96 (lH, d, J=3Hz)

## Claims

**1.** A compound of the formula :

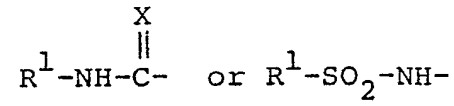


wherein
$R^1$-A- is a group of the formula :



in which
$R^1$ is aryl or a heterocyclic group, each of which may be substituted with substituent(s) selected from the group consisting of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkylthio, halo($C_1$-$C_6$)alkyl, acyl, acylamino and halogen, or $C_1$-$C_6$ alkyl which may be substituted with a heterocyclic group optionally substituted with acyl, and
X is O or S, and

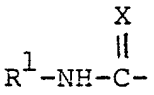
$R^2$ is hydrogen or $C_1$-$C_6$ alkyl,
provided that when $R^1$ is $C_1$-$C_6$ alkyl, then
$R^1$-A- is a group of the formula :



in which $R^1$ and X are each as defined above, and pharmaceutically acceptable salts thereof.

**2.** A compound of claim 1, wherein
$R^1$ is phenyl, naphthyl, pyridyl, imidazolyl, thienyl, quinolyl, benzothienyl or benzothiazolyl, each of which may be substituted with substituent(s) selected from the group consisting of $C_1$-$C_6$ alkyl,$C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkylthio, halo($C_1$-$C_6$)alkyl, $C_1$-$C_6$ alkoxycarbonyl, $C_1$-$C_6$ alkanoylamino,$C_1$-$C_6$ alkylsulfonylamino and halogen, or $C_1$-$C_6$ alkyl which may be substituted with imidazolyl optionally substituted with $C_1$-$C_6$ alkoxycarbonyl.

**3.** A compound of claim 2, wherein
$R^1$-A- is a group of the formula :

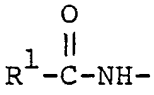


in which
$R^1$ is phenyl, naphthyl, $C_1$-$C_6$ alkylphenyl, $C_1$-$C_6$ alkoxyphenyl, $C_1$-$C_6$ alkylthiophenyl, mono or dihalophenyl, halo($C_1$-$C_6$)alkylphenyl, $C_1$-$C_6$ alkanoylaminophenyl, $C_1$-$C_6$ alkylsulfonylaminophenyl, halogen and halo($C_1$-$C_6$)alkyl substituted phenyl, $C_1$-$C_6$ alkoxy and halo-($C_1$-$C_6$)alkyl substituted phenyl, pyridyl, benzo[b]thienyl or $C_1$-$C_6$ alkyl, and
X is O or S, and
$R^2$ is hydrogen.

**4.** A compound of claim 3, wherein
$R^1$ is phenyl, monohalophenyl, mono[halo($C_1$-$C_6$)alkyl]phenyl or mono($C_1$-$C_6$)-alkylsulfonylaminophenyl.

**5.** A compound of claim 4, which is
disodium salt of [N-(phenyl)thiocarbamoylmethylene]bis(phosphonic acid).

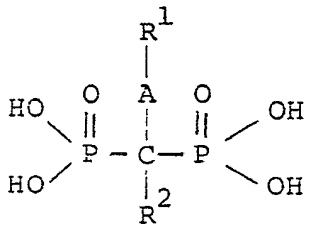
**6.** A compound of claim 2, wherein
$R^1$-A- is a group of the formula :



**7.** A compound of claim 2, wherein
$R^1$-A- is a group of the formula :

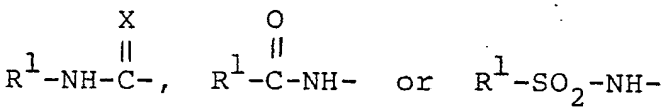
$R^1$-$SO_2$-NH-

8. A process for preparing a compound of the formula :



wherein

$R^1$-A- is a group of the formula :



in which

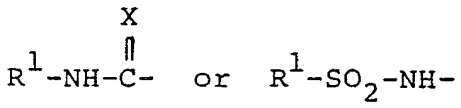
$R^1$ is aryl or a heterocyclic group, each of which may be substituted with substituent(s) selected from the group consisting of $C_1$-$C_6$ alkyl, $C_1$-$C_6$ alkoxy, $C_1$-$C_6$ alkylthio, halo($C_1$-$C_6$)alkyl, acyl, acylamino and halogen, or $C_1$-$C_6$ alkyl which may be substituted with a heterocyclic group optionally substituted with acyl, and

X is O or S, and

$R^2$ is hydrogen or $C_1$-$C_6$ alkyl,

provided that when $R^1$ is $C_1$-$C_6$ alkyl, then

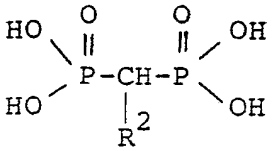
$R^1$-A- is a group of the formula :



in which $R^1$ and X are each as defined above,

or its salt, which comprises

a) reacting a compound of the formula :

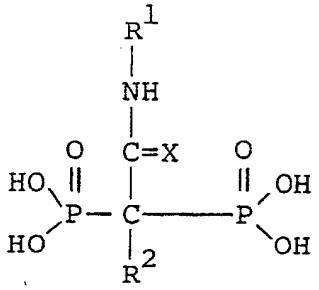


wherein $R^2$ is as defined above,

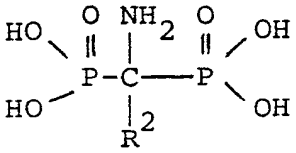
or its salt with a compound of the formula :

$R^1$-NCX

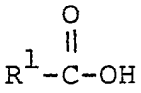
wherein $R^1$ and X are each as defined above, or its equivalent or a salt thereof to give a compound of the formula :



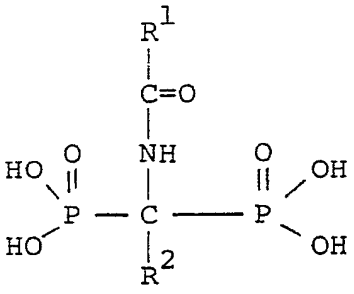
wherein $R^1$, $R^2$ and X are each as defined above,
or its salt, or
b) reacting a compound of the formula :



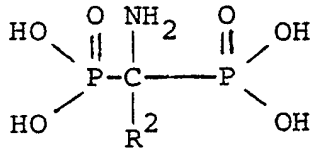
wherein $R^2$ is as defined above,
or its reactive derivative at the amino group
or its salt with a compound of the formula:



wherein $R^1$ is as defined above,
or its reactive derivative at the carboxy group
or its salt to give a compound of the formula :



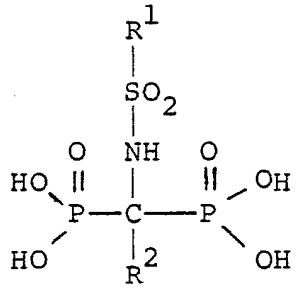
wherein $R^1$ and $R^2$ are each as defined above,
or its salt, or
c) reacting a compound of the formula :



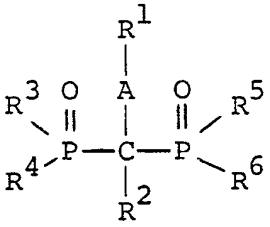
wherein $R^2$ is as defined above, or its reactive derivative at the amino group or its salt with a compound of the formula :

$R^1$-$SO_2$-OH

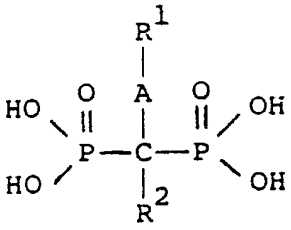
wherein $R^1$ is as defined above,
or its reactive derivative at the sulfo group
or its salt to give a compound of the formula:



wherein $R^1$ and $R^2$ are each as defined above,
or its salt, or
d) subjecting a compound of the formula :



wherein $R^3$, $R^4$, $R^5$ and $R^6$ are each protected hydroxy, and
$R^1$-A- and $R^2$ are each as defined above, or its salt to elimination reaction of the hydroxy-protective group to give a compound of the formula :



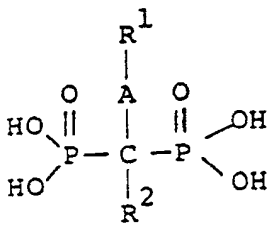
wherein $R^1$-A- and $R^2$ are each as defined above, or its salt.

9. A pharmaceutical composition comprising, as an active ingredient, a compound of claim 1 or pharmaceutically acceptable salts thereof in association with pharmaceutical carrier.

10. A compound of claim 1 for use as a medicament.

**Revendications**

1. Composé répondant à la formule :



dans laquelle $R^1$-A- est un groupe répondant à la formule:

$$R^1\text{-}NH\text{-}\overset{\overset{X}{\|}}{C}\text{-}, \quad R^1\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-} \text{ ou } \quad R^1\text{-}SO_2NH\text{-}$$

dans laquelle

$R^1$ est un groupe aryle ou un groupe hétérocyclique, chacun d'eux pouvant être substitué par un ou plusieurs substituants choisis parmi les groupes alkyle en $C_1$ à $C_6$, alcoxy en $C_1$ à $C_6$, alkylthio en $C_1$ à $C_6$, haloalkyle en $C_1$ à $C_6$, acyle, acylamino et un atome d'halogène, ou un groupe alkyle en $C_1$ à $C_6$ qui peut être substitué par un groupe hétérocyclique substitué si on le désire par un groupe acyle, et

X est O ou S, et

$R^2$ est un atome d'hydrogène ou un groupe alkyle en $C_1$ à $C_6$,

sous réserve que lorsque $R^1$ est un groupe alkyle en $C_1$ à $C_6$,

$R^1$-A- est un groupe répondant aux formules :

$$R^1\text{-}NH\text{-}\overset{\overset{X}{\|}}{C}\text{-} \text{ ou } R^1\text{-}SO_2\text{-}NH\text{-}$$

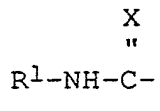
dans lesquelles $R^1$ et X sont chacun tels que définis ci-dessus.

et ses sels pharmaceutiquement acceptables.

2. Composé selon la revendication 1, dans lequel :

$R^1$ est un groupe phényle, naphtyle, pyridyle, imidazolyle, thiényle, quinolyle, benzothiényle ou benzothiazolyle, chacun d'eux pouvant être substitué par un ou plusieurs substituants choisis parmi les groupes alkyle en $C_1$ à $C_6$, alcoxy en $C_1$ à $C_6$, alkylthio en $C_1$ à $C_6$, haloalkyle en $C_1$ à $C_6$ (alcoxy en $C_1$ à $C_6$)carbonyle, alcanoylamino en $C_1$ à $C_6$, alkylsulfonylamino en $C_1$ à $C_6$ et un atome d'halogène, ou un groupe alkyle en $C_1$ à $C_6$ qui peut être substitué par un groupe imidazolyle substitué si on le désire par un groupe (alcoxy en $C_1$ à $C_6$)carbonyle.

3. Composé selon la revendication 2, dans lequel $R^1$-A- est un groupe répondant à la formule :



dans laquelle :

$R^1$ est un groupe phényle, naphtyle, (alkyle en $C_1$ à $C_6$) phényle, (alcoxy en $C_1$ à $C_6$)phényle, (alkyle en $C_1$ à $C_6$)thiophényle, mono- ou dihalophényle, halo(alkyle en $C_1$ à $C_6$)phényle, (alcanoylamino en $C_1$ à $C_6$)phényle (alkyle en $C_1$ à $C_6$)sulfonylaminophényle, phényle substitué par un atome d'halogène et un groupe haloalkyle en $C_1$ à $C_6$, phényle substitué par un groupe alcoxy en $C_1$ à $C_6$ et un groupe halo(alkyle en $C_1$ à $C_6$), pyridyle, benzo[b]thiényle ou alkyle en $C_1$ à $C_6$ et

X est O ou S, et

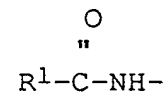
$R^2$ est un atome d'hydrogène.

**4.** Composé selon la revendication 3, dans lequel :

$R^1$ est un groupe phényle, monohalophényle, mono[halo(alkyle en $C_1$ à $C_6$)]-phényle, ou mono-(alkyle en $C_1$ à $C_6$)sulfonylaminophényle.

**5.** Composition selon la revendication 4, qui est le se disodique d'un acide [N-(phényl)-thiocarbamoylméthylène]-bis(phosphonique).

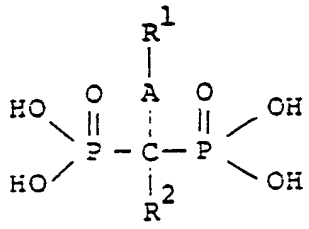
**6.** Composé selon la revendication 2, dans lequel $R^1$-A- est un groupe répondant à la formule :



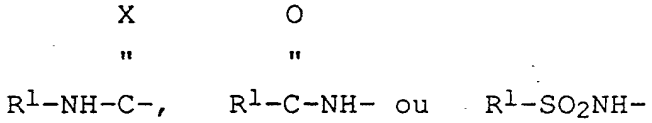
**7.** Composé selon la revendication 2, dans lequel $R^1$-A- est un groupe répondant à la formule :

$R^1$-$SO_2$-NH-

**8.** Procédé de préparation d'un composé répondant à la formule :



dans laquelle $R^1$-A- est un groupe répondant à la formule:



dans laquelle

$R^1$ est un groupe aryle ou un groupe hétérocyclique, chacun d'eux pouvant être substitué par un ou plusieurs substituants choisis parmi les groupes alkyle en $C_1$ à $C_6$, alcoxy en $C_1$ à $C_6$, alkylthio en $C_1$ à $C_6$, haloalkyle en $C_1$ à $C_6$, acyle, acylamino et un atome d'halogène, ou un

groupe alkyle en $C_1$ à $C_6$ qui peut être substitué par un groupe hétérocyclique substitué si on le désire par un groupe acyle, et

X est O ou S, et

$R^2$ est un atome d'hydrogène ou un groupe alkyle en $C_1$ à $C_6$,

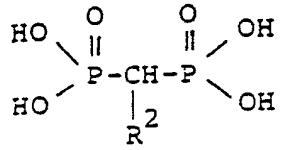
sous réserve que lorsque $R^1$ est un groupe alkyle en $C_1$ à $C_6$,

$R^1$-A- est un groupe répondant à la formule :

dans laquelle $R^1$ et X sont chacun tels que définis ci-dessus.

et son sel, qui comprend :

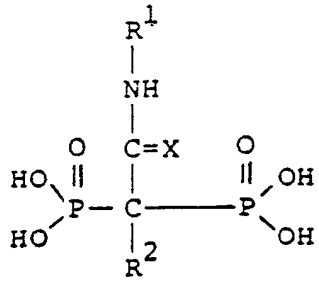
a) le fait de faire réagir un composé répondant à la formule :



dans laquelle $R^2$ est tel que défini ci-dessus, ou son sel, avec un composé répondant à la formule :

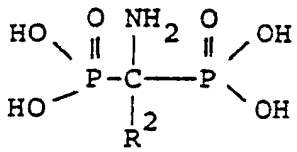
$R^1$ -NCX

dans laquelle $R^1$ et X sont chacun tels que définis ci-dessus, ou son équivalent ou un de ses sels, pour donner un composé répondant à la formule :

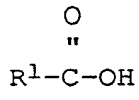


dans laquelle $R^1$, $R^2$ et X sont chacun tels que définis ci-dessus, ou son sel, ou

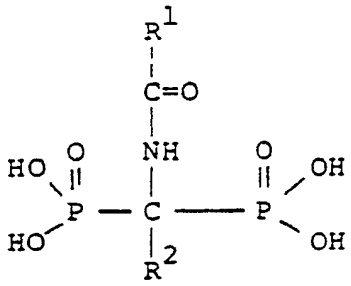
b) le fait de faire réagir un composé répondant à la formule :



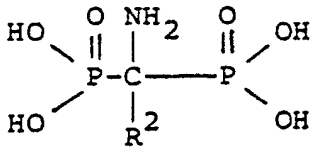
dans laquelle $R^2$ est tel que défini ci-dessus, ou son dérivé réactif sur le groupe amino ou son sel, avec un composé répondant à la formule :



dans laquelle $R^1$ est tel que défini ci-dessus, ou son dérivé réactif sur le groupe carboxy ou son sel, pour donner un composé répondant à la formule :



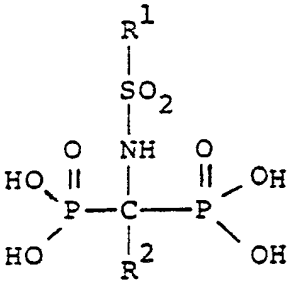
dans laquelle $R^1$ et $R^2$ sont chacun tels que définis ci-dessus, ou son sel, ou
c) le fait de faire réagir un composé répondant à la formule :



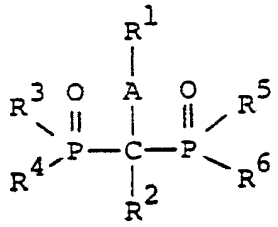
dans laquelle $R^2$ est tel que défini ci-dessus, ou son dérivé réactif sur le groupe amino ou son sel, avec un composé répondant à la formule :

$R^1$-$SO_2$-OH

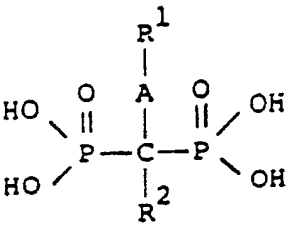
dans laquelle $R^1$ est tel que défini ci-dessus, ou son dérivé réactif sur le groupe sulfo ou son sel,pour donner un composé répondant à la formule :



dans laquelle $R^1$ et $R^2$ sont chacun tels que définis ci-dessus, ou son sel, ou
d) le fait de soumettre un composé répondant à la formule :



dans laquelle $R^3$, $R^4$, $R^5$ et $R^6$ sont chacun un groupe hydroxy protégé, et
$R^1$-A- et $R^2$ sont chacun tels que définis ci-dessus, ou son sel, à une réaction d'élimination du groupe protecteur du groupe hydroxy, pour donner un composé répondant à la formule :



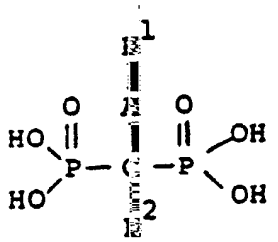
dans laquelle $R^1$-A- et $R_2$ sont chacun tels que définis ci-dessus, ou son sel.

9. Composition pharmaceutique comprenant comme ingrédient actif un composé selon la revendication 1 ou ses sels pharmaceutiquement acceptables en association avec un support pharmaceutique.

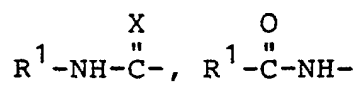
10. Composé selon la revendication 1, pour l'utilisation comme médicament.

**Ansprüche**

1. Verbindung der Formel:

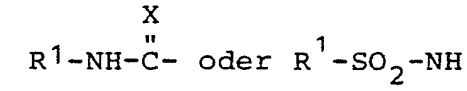


worin bedeuten:
$R^1$-A- eine Gruppe der Formel



oder $R^1$-$SO_2$-NH-worin $R^1$ für Aryl oder eine heterocyclische Gruppe steht, von denen jede substituiert sein kann durch einen oder mehr Substituenten, ausgewählt aus der Gruppe, die besteht aus $C_1$-$C_6$-Alkyl, $C_1$-$C_6$-Alkoxy, $C_1$-$C_6$-Alkylthio, Halogen($C_1$-$C_6$)alkyl, Acyl, Acylamino und Halogen, oder für $C_1$-$C_6$-Alkyl steht, das substituiert sein kann durch eine heterocyclische Gruppe, die gegebenenfalls durch Acyl substituiert ist, und X für O oder S steht und

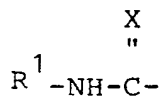
$R^2$ Wasserstoff oder $C_1$-$C_6$-Alkyl,
mit der Maßgabe, daß dann, wenn $R^1$ für $C_1$-$C_6$-Alkyl steht, $R^1$-A eine Gruppe der Formel darstellt



worin $R^1$ und X jeweils wie oben definiert sind, und ihre pharmazeutisch akzeptablen Salze.

2. Verbindung nach Anspruch 1, worin $R^1$ für Phenyl, Naphthyl, Pyridyl, Imidazolyl, Thienyl, Chinolyl, Benzothienyl oder Benzothiazolyl steht, von denen jedes substituiert sein kann durch einen oder mehrere Substituenten, ausgewählt aus der Gruppe, die besteht aus $C_1$-$C_6$-Alkyl, $C_1$-$C_6$-Alkoxy, $C_1$-$C_6$-Alkylthio, Halogen($C_1$-$C_6$)alkyl, $C_1$-$C_6$-Alkoxycarbonyl, $C_1$-$C_6$-Alkanoylamino, $C_1$-$C_6$-Alkylsulfonylamino und Halogen oder steht für $C_1$-$C_6$-Alkyl, das substituiert sein kann durch Imidazolyl, das gegebenenfalls durch $C_1$-$C_6$-Alkoxycarbonyl substituiert ist.

3. Verbindung nach Anspruch 2, worin $R^1$-A für eine Gruppe der Formel steht



worin bedeuten:

$R^1$ Phenyl, Naphthyl, $C_1$-$C_6$-Alkylphenyl, $C_1$-$C_6$-Alkoxyphenyl, $C_1$-$C_6$-Alkylthiophenyl, Mono- oder Dihalogenphenyl, Halogen-($C_1$-$C_6$)alkylphenyl, $C_1$-$C_6$-Alkanoylaminophenyl, $C_1$-$C_6$-Alkylsulfonylaminophenyl, Halogen- und Halogen($C_1$-$C_6$)alkyl-substituiertes Phenyl, $C_1$-$C_6$-Alkoxy- und Halogen($C_1$-$C_6$)alkylsubstituiertes Phenyl, Pyridyl, Benzo[b]thienyl oder $C_1$-$C_6$-Alkyl und

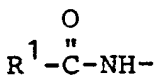
X O oder S und

$R^2$ Wasserstoff.

4. Verbindung nach Anspruch 3, worin $R^1$ für Phenyl, Monohalogenphenyl, Mono[halogen($C_1$-$C_6$)alkyl]-phenyl oder Mono-($C_1$-$C_6$)alkylsulfonylaminophenyl steht.

5. Verbindung nach Anspruch 4, bei der es sich handelt um das Dinatriumsalz der [N-(Phenyl)-thiocarbamoylmethylen]bis(phosphonsäure).

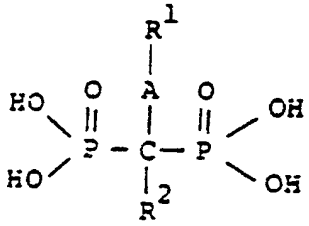
6. Verbindung nach Anspruch 2, worin $R^1$-A für eine Gruppe der Formel steht:



7. Verbindung nach Anspruch 2, worin $R^1$-A- für eine Gruppe der Formel steht:

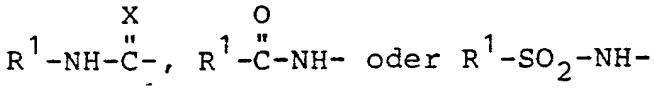
$R^1$-$SO_2$-NH-

8. Verfahren zur Herstellung einer Verbindung der Formel:



worin bedeuten:

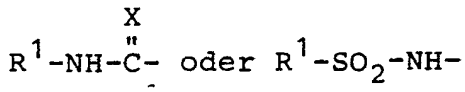
$R^1$-A- eine Gruppe der Formel



worin $R^1$ für Aryl oder eine heterocyclische Gruppe steht, von denen jede substituiert sein kann durch einen oder mehrere Substituenten, ausgewählt aus der Gruppe, die besteht aus $C_1$-$C_6$-Alkyl, $C_1$-$C_6$-Alkoxy, $C_1$-$C_6$-Alkylthio, Halogen($C_1$-$C_6$)alkyl, Acyl, Acylamino und Halogen, oder steht für $C_1$-$C_6$-Alkyl, das substituiert sein kann durch eine heterocyclische Gruppe, die gegebenenfalls durch Acyl substituiert ist, und X für O oder S steht, und

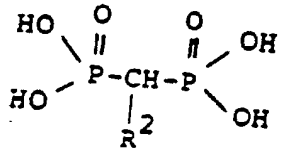
$R^2$ Wasserstoff oder $C_1$-$C_6$-Alkyl,

mit der Maßgabe, daß dann, wenn $R^1$ für $C_1$-$C_6$-Alkyl steht, $R^1$-A- eine Gruppe der Formel darstellt



worin $R^1$ und X jeweils wie oben definiert sind, oder ihres Salzes, das umfaßt

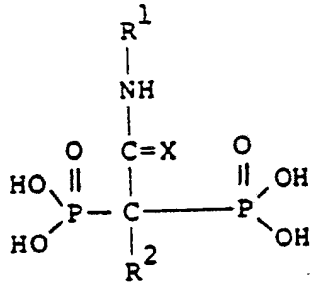
(a) die Umsetzung einer Verbindung der Formel:



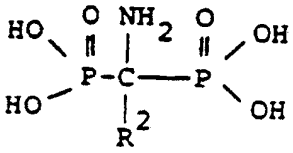
worin $R^2$ wie oben definiert ist, oder ihres Salzes mit einer Verbindung der Formel:

$R^1$-NCX

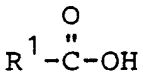
worin $R^1$ und X jeweils wie oben definiert sind, oder ihrem Äquivalent oder einem Salz derselben unter Bildung einer Verbindung der Formel:



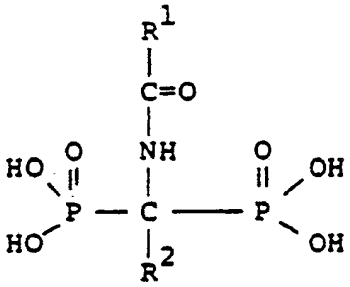
worin $R^1$, $R^2$ und X jeweils wie oben definiert sind, oder ihres Salzes, oder
(b) die Umsetzung einer Verbindung der Formel:



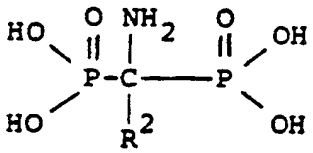
worin $R^2$ wie oben definiert ist, oder ihres reaktionsfähigen Derivats an der Aminogruppe oder ihres Salzes mit einer Verbindung der Formel:



worin $R^1$ wie oben definiert ist, oder ihrem reaktionsfähigen Derivat an der Carboxygruppe oder ihrem Salz unter Bildung einer Verbindung der Formel:



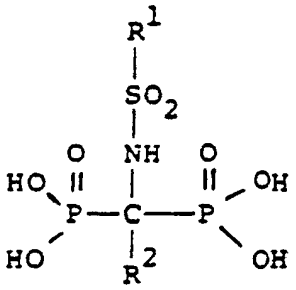
worin $R^1$ und $R^2$ jeweils wie oben definiert sind, oder ihres Salzes, oder
(c) die Umsetzung einer Verbindung der Formel:



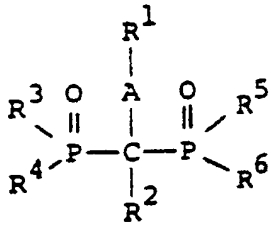
worin $R^2$ wie oben definiert ist, oder ihres reaktionsfähigen Derivats an der Aminogruppe oder ihres Salzes mit einer Verbindung der Formel:

$R^1$-$SO_2$-OH

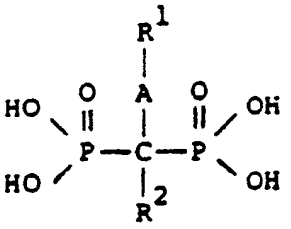
worin $R^1$ wie oben definiert ist, oder ihrem reaktionsfähigen Derivat an der Sulfogruppe oder ihrem Salz unter Bildung einer Verbindung der Formel:



worin $R^1$ und $R^2$ jeweils wie oben definiert sind, oder ihres Salzes, oder
(d) die Durchführung einer Reaktion zur Eliminierung der Hydroxyschutzgruppe aus einer Verbindung der Formel:



worin $R^3$, $R^4$, $R^5$ und $R^6$ jeweils geschütztes Hydroxy bedeuten und $R^1$-A- und $R^2$ jeweils wie oben definiert sind, oder ihrem Salz unter Bildung einer Verbindung der Formel:



worin $R^1$-A- und $R^2$ jeweils wie oben definiert sind, oder ihres Salzes.

9. Pharmazeutische Zusammensetzung, die als aktive Komponente eine Verbindung nach Anspruch 1 oder pharmazeutisch akzeptable Salze derselben in Assoziation mit einem pharmazeutischen Träger enthält.

10. Verbindung nach Anspruch 1 für die Verwendung als Arzneimittel.